AHRQ Systematic Review Surveillance Program

CER #053: Treatment to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis: Update of a 2007 Report

Original Release Date: March 2012
Surveillance Report: August 2016

Summary of Key Findings from Surveillance Report:

- Key Question 1: New studies were identified evaluating exercise and NSAIDs for fracture risk reduction; however, the new evidence does not change the conclusions of the original systematic review.
- Key Question 2: New studies were identified evaluating denosumab for the treatment of high risk postmenopausal women with osteoporosis with no adjustment for those with renal impairment; however, the new evidence does not change the conclusions of the original systematic review.
- Key Question 3: The conclusions in the original systematic review are likely current.
- Key Question 4: New RCTs and observational studies have reported many adverse events that the original systematic review did not report or for which they reported insufficient evidence. Conclusions related to the risk of cerebrovascular accident, myocardial infarctions, GI events, death, arrhythmia, dyspnea, and hypertension while taking teriparatide; the risk of headaches and dizziness, arthritis and arthralgia, and hypotension while taking raloxifene; and the risk of

dermatological conditions and falling while taking denusomab may not be current. Conclusions related adverse events while taking bisphosphonates, hormone replacement therapy, vitamin D, and calcium are likely current.

- Key Question 5a: The conclusions in the original systematic review are likely current.
- Key Question 5b: The conclusions in the original systematic review are likely current.

Signal Assessment: The signal is medium and suggests that portions of the original review may not be current.

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Conflict of Interest:
None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Table of Contents

Introduction

The purpose of the surveillance process for the Evidence-based Practice Center (EPC) Program is to determine whether the conclusions of a systematic review are current. The surveillance process examines the conclusions to the key questions as written, and does not evaluate the currency of the original scope (i.e., key questions, included interventions). Approximately 25 systematic reviews are selected for surveillance annually based on popularity, use in obtaining continuing medical education certificates, potential impact for changing the field, and use in clinical practice guidelines.

CER #053, *Treatment to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis: Update of a 2007 Report,*[1] was originally released in March 2012.

The key questions for the original systematic review are as follows:

Key Question 1. What are the comparative benefits in fracture risk reduction among the following therapeutic modalities for low bone density:

- Bisphosphonate medications, specifically:
  - Alendronate (Fosamax®, oral)
  - Risedronate (Actonel®; oral once-a-week)
  - Ibandronate (Boniva®)
  - Zoledronic acid (Reclast®IV).
- Denosumab (Prolia®)
- Menopausal estrogen therapy for women (numerous brands and routes of administration)
- Parathyroid hormone (PTH)
  - 1-34 (teriparatide) (Forteo®)
- Selective estrogen receptor modulators (SERMs), specifically:
  - Raloxifene (Evista®)
- Calcium
- Vitamin D
- Combinations or sequential use of above
- Exercise in comparison to above agents

Key Question 2. How does fracture risk reduction resulting from treatments vary between individuals with different risks for fracture as determined by the following factors:

- Bone mineral density
- FRAX or other risk assessment score
- Prior fractures (prevention vs. treatment)
- Age
- Sex
- Race/ethnicity
- Glucocorticoid use
- Other factors (e.g., whether the individuals were community dwelling vs. institutionalized, vitamin D deficient vs. not)

Key Question 3: Regarding treatment adherence and persistence,

- What are the levels of adherence to and persistence with medications for the treatment and prevention of osteoporosis?

- What factors affect adherence and persistence?

Key Question 4: What are the short- and long-term harms (adverse effects) of the above therapies (when used specifically to treat or prevent low bone density/osteoporotic fracture), and do these vary by any specific subpopulations (e.g., the subpopulations identified in Key Question 2)?

Key Question 5: With regard to treatment for preventing osteoporotic fracture:

a. How often should patients be monitored (via measurement of bone mineral density) during therapy, how does bone density monitoring predict antifracture benefits during pharmacotherapy, and does the ability of monitoring to predict antifracture effects of a particular pharmacologic agent vary among the pharmacotherapies?
b. How does the antifracture benefit vary with long-term continued use of pharmacotherapy, and what are the comparative antifracture effects of continued long-term therapy with the various pharmacotherapies?

Our surveillance assessment began in May 2016. We conducted an electronic search for literature published since the end date of the original systematic review. After completing a scan of this literature to identify evidence potentially related to the key questions in this systematic review, we contacted experts involved in the original systematic review to request their opinions as to whether the conclusions had changed.

Methods

Literature Searches

We conducted a literature search of PubMed covering August 2009 to May 2016 using the identical search strategy used for the original review[1] and searching for studies published since the end date of the original systematic review.

The search was conducted to assess the currency of conclusions. This process included selecting journals from among the top 10 journals from relevant specialty subject areas (derived by searching ISI's Journal Citation Reports by relevant disciplinary fields and sorting the results by five-year average impact factor from highest to lowest; Appendix A), and among those most highly represented among the references for the original review (Appendix B). The included journals were ten high-profile general medical interest journals (Annals of Internal Medicine, Archives of Internal Medicine, BMC Medicine, The BMJ, JAMA, JAMA Internal Medicine, Journal of Cachexia, Lancet, New England Journal of Medicine, PLOS Medicine, Sarcopenia and Muscle) and ten specialty journals (The American Journal of Sports Medicine, Arthroscopy: The Journal of Arthroscopic and Related Surgery, Clinical Orthopaedics and Related Research, The Journal of the American Academy of Orthopaedic Surgeons, The Journal of Bone and Joint Surgery: American Volume, The Journal of Bone and Joint Surgery: British Volume, The Journal of Orthopaedic and Sports Physical Therapy, Journal of Physiotherapy, Osteoarthritis and Cartilage, and Physical Therapy). The search strategy is reported in Appendix C.

Study Selection

Using the same inclusion and exclusion criteria as the original systematic review (see Appendix D), one investigator reviewed the titles and abstracts of the 20 high-impact journal search

results (Appendix E). We included systematic reviews and meta-analyses, whether or not they were included (as a study design) in the original systematic reviews. For systematic reviews and meta-analyses, we considered findings only if all included studies met criteria that a) all studies were not included or excluded from the original systematic review, b) all studies were not included in a prior surveillance report (if applicable), and c) all studies met inclusion criteria for the original systematic review. Reviews for which one or more study did not meet our criteria were used to identify potentially relevant primary research. For searches identifying greater than 200 unique titles, we randomly selected a total of 200 articles to examine. For searches identifying greater than 200 unique titles, we randomly selected a total of 200 articles to examine in our assessment of the currency of conclusions in the original systematic review.

Expert Opinion

We shared the conclusions of the original systematic review and most recent surveillance assessment, findings from the literature analysis, and the newly identified studies with 14 experts in the field (11 original peer reviewers, 2 technical expert panel members [TEP], and 1 local expert) to request their assessment of the currency of original review conclusions and their recommendations of any relevant new studies. Two subject matter experts responded to our request. Appendix F shows the form experts were asked to complete.

FDA, Health Canada, and MHRA Warnings

We searched the Food and Drug Administration (FDA) MedWatch online database, Health Canada, and MHRA websites for black box warnings relevant to the key questions in this systematic review.

Check for Qualitative Signals

The authors of the original systematic review conducted a qualitative synthesis of data on three main aspects: one to evaluate efficacy and effectiveness, one to evaluate adherence, and one to evaluate adverse events. Comparisons of interest for all analyses were single drug versus placebo for each of the drugs of interest, and single drug versus single drug comparisons for drugs within the same class and across classes. In addition, the authors evaluated comparisons between estrogen combined with progesterone and placebo or single drugs. Studies that included either calcium or vitamin D in both study arms were classified as being comparisons between the other agents in each arm, e.g., alendronate plus calcium versus risedronate plus calcium would be classified as alendronate versus risedronate. The outcome of interest for assessing effectiveness for this report is fractures, based on FDA requirements. To assess adherence, the authors extracted reported rates of adherence or persistence from trials and observational studies separately, as the rates of adherence and persistence reported for trials are likely to be higher than would be observed in practice. For adverse events, two main analyses were performed: analyses to assess the relationship between a group of adverse events that were identified a priori as particularly relevant and exploratory analyses of all adverse events that were reported for any of the drugs. We compared the conclusions of the included abstracts to the conclusions of the original systematic review and assessed expert input, and FDA alert information to identify qualitative signals about the currency of conclusions.

Compilation of Findings and Conclusions

For this assessment we constructed a summary table (Appendix G) that includes the key questions and conclusions from the original systematic review, findings of the new literature search, FDA black box warnings, and the expert assessments that pertained to each key question. Because we did not find any FDA, Heath Canada, or MHRA black box warnings relevant to the key questions in this systematic review, we did not include a column for this in the summary table. We categorized the currency of conclusions using a 3-category scheme:

- Original conclusion is still valid and this portion of the systematic review is likely current
- Original conclusion is possibly out of date and this portion of the systematic review may not be current
- Original conclusion is out of date.

We considered the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the systematic review conclusion as still valid, we classified the systematic review conclusion as likely current.
- If we found some new evidence that might change the systematic review conclusion, and /or a minority of responding experts assessed the systematic review conclusion as having new evidence that might change the conclusion, then we classified the systematic review conclusion as possibly not current.
- If we found new evidence that rendered the systematic review conclusion out of date or no longer applicable, we classified the systematic review conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from the FDA, Health Canada, or MHRA equivalent, etc.

Signal Assessment for Currency of the Systematic Review

We used the following considerations in our assessment of currency of the systematic review:

- **Strong signal:** A report is considered to have a strong signal if new evidence is identified that clearly renders conclusions from the original systematic review out of date, such as the addition or removal of a drug or device from the market or a new FDA boxed warning.
- **Medium signal:** A report is considered to have a medium signal when new evidence is identified which may change the conclusions from the original systematic review. This may occur when abstract review and expert assessment indicates that some conclusions from the original systematic review may not be current, or when it is unclear from abstract review how new evidence may impact the findings from the original systematic review.
- **Weak signal:** A report is considered to have a weak signal if no new evidence is identified that would change the conclusions from the original systematic review. This may occur when no new evidence is identified, or when some new evidence is identified but it is clear from abstract review and expert assessment that the new evidence is unlikely to change the conclusions of the original systematic review.

Results

Literature Search

The literature search identified 2,787 unique titles from the 10 selected high profile general medical and specialty journals. We examined a random selection of 200 of the 2,787 articles (see Appendix E). Upon abstract review, 195 of the randomly selected studies were rejected because they did not meet the original systematic review inclusion criteria (see Appendix D). The remaining 5 studies[2-6] were examined for potential to change the results of the original systematic review.

FDA, Health Canada, and MHRA Warnings

We did not find any FDA black box warnings (or class I device recalls and withdrawals) relevant to the key questions in this systematic review.

Expert Opinion

We shared the conclusions of the original review with 14 experts in the field (11 original peer reviewers, 2 TEP members, and 1 local expert) to request their assessment of the currency of systematic review conclusions and their recommendations of any relevant new studies. Two subject matter experts responded.

One expert believed all conclusions to be current, but mentioned that trials with bone mineral density as an endpoint may provide useful information. Additionally, this reviewer suggested two studies that looked at rates of adherence (KQ 3) and zoledronic acid in elderly women (KQ 4). The latter was included (see Appendix G) and its findings failed to disagree with the original conclusions.

The second reviewer believed all conclusions to be current, but mentioned that there is now FDA approval for another SERM, Bazedoxifene, but only in conjunction with conjugated estrogens and for the prevention of postmenopausal osteoporosis. The expert added that there is not yet evidence for preventing fractures and it is therefore not approved to prevent fractures.

Identifying Qualitative Signals

Appendix G shows the original key questions, the conclusions of the original systematic review, the results of the literature search, expert opinion, and the assessment of the currency of the systematic review.

For key question 1, regarding the effects of various treatments of fracture risk reduction, though all original systematic review conclusions are likely current, additional information was identified with use of exercise as treatment and NSAIDs/Paracetamol/opioid use. A significantly higher number of vertebral compression fractures occur in patients with postmenopausal osteoporosis who followed a flexion exercise program compared with those using extension exercises, and individuals receiving NSAIDs sustained more fractures than comparators and paracetamol and opioids were associated with a non-significant trend towards more fractures. The conclusions from the original systematic review for key question 2 are likely current, however our literature search found that denosumab recently received regulatory approval for the treatment of high risk postmenopausal women with osteoporosis with no adjustment for those with renal impairment. The original systematic review conclusions for key question 3, which examined the

prevalence of adherence, various factors that affect adherence, and its impact on the effectiveness of medication, are likely current.

Key question 4 examines the short- and long-term harms of various therapies for low bone density and/or osteoporotic fracture. While only one pooled analysis from the original systematic review identified an adverse event (headaches) for teriparatide, our literature search found one prospective observational study that reported the additional following harms for teriparatide: risk of cerebrovascular accident, myocardial infarction, nausea, death, transient ischemic attack, arrhythmia, dyspnea, and hypertension. Additionally, the original systematic review found no significant effect on reports of arthritis and arthralgia with use of raloxifene and found no studies on the incidences of dizziness or hypotension with raloxifene, whereas our updated literature search identified one double-blind RCT which reported significant incidences of arthralgia, dizziness, and hypotension with raloxifene use. The original systematic review did not report incidences of dermatological conditions and falling as adverse events while using pharmacotherapy. Our literature search identified a three-year randomized, placebo-controlled clinical trial of 60 mg of denosumab wherein the treatment group reported a significant increase in the risk of eczema and cellulitis as well as a significant decrease in the risk of falling and concussions. Therefore, the conclusions of the original systematic review may be out of date.

All conclusions related to key question 5 are likely current. Additionally, there were no FDA black box, Health Canada, or MHRA health warnings identified since the original systematic review was published.

Signal Assessment

The SRC conclusions based on the results of the prior surveillance assessment, literature published since the original report, FDA black box warnings, and expert assessment is that:

- Key Question 1: New studies were identified evaluating exercise and NSAIDs for fracture risk reduction; however, the new evidence does not change the conclusions of the original systematic review.
- Key Question 2: New studies were identified evaluating denosumab for the treatment of high risk postmenopausal women with osteoporosis with no adjustment for those with renal impairment; however, the new evidence does not change the conclusions of the original systematic review.
- Key Question 3: The conclusions in the original systematic review are likely current.
- Key Question 4: New RCTs and observational studies have reported many adverse events that the original systematic review did not report or for which they reported insufficient evidence. Conclusions related to the risk of cerebrovascular accident, myocardial infarctions, GI events, death, arrhythmia, dyspnea, and hypertension while taking teriparatide; the risk of headaches and dizziness, arthritis and arthralgia, and hypotension while taking raloxifene; and the risk of dermatological conditions and falling while taking denusomab may not be current. Conclusions related adverse events while taking bisphosphonates, hormone replacement therapy, vitamin D, and calcium are likely current.
- Key Question 5a: The conclusions in the original systematic review are likely current.
- Key Question 5b: The conclusions in the original systematic review are likely current.

The signal for this report is medium suggesting that the portions of the original systematic review may be out of date.

References

1. Crandall CJ, Newberry SJ, Diamant A, et al. AHRQ Comparative Effectiveness Reviews. *Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.

2. Fahrleitner-Pammer A, Langdahl BL, Marin F, et al. Fracture rate and back pain during and after discontinuation of teriparatide: 36-month data from the European Forsteo Observational Study (EFOS). *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Oct 2011;22(10):2709-2719.

3. Lewiecki EM. Clinical use of denosumab for the treatment for postmenopausal osteoporosis. *Current medical research and opinion.* Dec 2010;26(12):2807-2812.

4. Lufkin EG, Whitaker MD, Nickelsen T, et al. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research.* Nov 1998;13(11):1747-1754.

5. Sinaki M, Mikkelsen BA. Postmenopausal spinal osteoporosis: flexion versus extension exercises. *Archives of physical medicine and rehabilitation.* Oct 1984;65(10):593-596.

6. Vestergaard P, Hermann P, Jensen JE, Eiken P, Mosekilde L. Effects of paracetamol, non-steroidal anti-inflammatory drugs, acetylsalicylic acid, and opioids on bone mineral density and risk of fracture: results of the Danish Osteoporosis Prevention Study (DOPS). *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Apr 2012;23(4):1255-1265.

Appendices

Appendix A. Top 10 Journals

In the Journal Citation Reports database, the science and social science sections were searched by subject area discipline(s) for each surveillance reports topic area. For each subject area discipline, the list was constructed by selecting the top 10 journals from the 5-year citation impact factor average list. Selected citations were downloaded in .csv format.

Top 10 Orthopedics:

1. The American Journal of Sports Medicine
2. Arthroscopy: The Journal of Arthroscopic and Related Surgery
3. Clinical Orthopaedics and Related Research
4. The Journal of the American Academy of Orthopaedic Surgeons
5. The Journal of Bone and Joint Surgery. American Volume
6. The Journal of Bone and Joint Surgery. British Volume
7. The Journal of Orthopaedic and Sports Physical Therapy
8. Journal of Physiotherapy
9. Osteoarthritis and Cartilage
10. Physical Therapy

Top 10 General Medical:

1. Annals of Internal Medicine
2. Archives of Internal Medicine
3. BMC Medicine
4. The BMJ
5. Journal of Cachexia, Sarcopenia and Muscle
6. JAMA Internal Medicine
7. JAMA
8. Lancet
9. New England Journal of Medicine
10. PLOS Medicine

Appendix B. Most Cited Journals from Original Systematic Review

Rank	Journal	# of Citations
1	Osteoporosis International	45
2	Journal of Bone and Mineral Research	28
3	Current Medical Research and Opinion	16
4	Bone	14
5	Journal of Bone and Mineral Metabolism	10
6	Journal of Clinical Endocrinology	9
7	Menopause	7
7	Clinical Therapy	7
9	The BMJ	6
10	Calcified Tissue International	4
10	Cochrane Database of Systematic Reviews	4
10	Journal of Rheumatology	4
10	JAMA	4
10	New England Journal of Medicine	4

Appendix C. Search Strategy

Database Searched: PubMed	
Date: May 19, 2016	
Original Search *	
1A (Bisphosphonates)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab NOT animal* NOT (human OR humans*) NOT mice OR mouse OR murine OR rat OR rats
OR	
1B (Serms)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND bisphosphonate* NOT animal* NOT (human OR humans*) NOT mice OR mouse OR murine OR rat OR rats
OR	
1C (Testosterone/Exercise)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND testosterone OR exercise* OR exercising OR physical activity OR “Exercise Therapy”[Mesh] NOT animal* NOT (human OR humans*) NOT mice OR mouse OR murine OR rat OR rats
OR	
1D (Other Treatments)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND strontium OR tibolone OR pth OR parathyroid hormone* OR “Estrogens”[Mesh] OR “Estrogens “[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR calcium OR vitamin d OR teriparatide OR forteo OR preos NOT animal* NOT (human OR humans*) NOT mice OR mouse OR murine OR rat OR rats
OR	

1E (Compliance)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND noncomplian* OR non-complian* OR nonadher* OR non-adher* OR refuse OR refusal OR treatment refusal OR patient compliance OR complian* OR comply OR complies OR complying OR adher* OR persistence NOT animal* NOT (human OR humans*) NOT mice OR mouse OR murine OR rat OR rats
OR	
4A (Efficacy)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND raloxifene* OR evista OR tamoxifen* OR nolvadex OR emblon OR fentamox OR soltamox OR tamofen OR bazedoxifene* OR lasofoxifene* OR selective estrogen receptor modulators OR serm OR serms
OR	
4B (Efficacy)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND strontium
OR	
4C (Efficacy)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND tibolone
OR	
4D (Efficacy)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND pth OR parathyroid hormone* NOT animal* NOT (human OR humans*) NOT mice OR mouse OR murine OR rat OR rats
OR	
4E (Efficacy)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND “Estrogens”[Mesh] OR “Estrogens “[Pharmacological Action] OR estrogen*[tiab] OR estradiol* NOT animal* NOT (human OR humans*)

	NOT mice OR mouse OR murine OR rat OR rats
OR	
4F (Efficacy)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND calcium NOT animal* NOT (human OR humans*) NOT mice OR mouse OR murine OR rat OR rats
OR	
4G (Efficacy)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND vitamin d NOT animal* NOT (human OR humans*) NOT mice OR mouse OR murine OR rat OR rats *
OR	
4H	teriparatide NOT pth OR parathyroid hormone*
OR	
5A (Compliance)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND noncomplian* OR non-complian* OR nonadher* OR non-adher* OR refuse OR refusal OR treatment refusal OR patient compliance OR complian* OR comply OR complies OR complying OR adher* OR persistence NOT animal* NOT (human OR humans*) NOT mice OR mouse OR murine OR rat OR rats
OR	
5B (Compliance Revision)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND noncomplian* OR non-complian* OR nonadher* OR non-adher* OR refuse OR refusal OR treatment refusal OR patient compliance OR complian* OR comply OR complies OR complying OR adher* OR persistence AND alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR

	aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab OR raloxifene* OR evista OR tamoxifen* OR nolvadex OR emblon OR fentamox OR soltamox OR tamofen OR bazedoxifene* OR lasofoxifene* OR selective estrogen receptor modulators OR serm OR serms OR calcium OR pth OR parathyroid hormone* OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR vitamin d OR testosterone OR exercise* OR exercising OR physical activity OR "Exercise Therapy"[Mesh] OR drug therapy OR drug[tiab] OR drugs[tiab] OR medication* OR therapy[tiab] OR therapies[tiab] OR treatment[tiab]
OR	
6A (Frax)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND frax
OR	
7 (Monitoring)	osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND monitor* NOT animal* NOT (human OR humans*) NOT mice OR mouse OR murine OR rat OR rats
OR	
8 (Related Articles)	Bell, K.J.L., "Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data." BMJ Online First, 2009. BMJ. 2009 Jun 23;338:b2266.
OR	
9A (Adverse Effects)	osteoporosis OR osteopenia OR osteopaenia OR fracture* OR bone mineral OR fractures[mh] OR bone density AND "adverse effects "[Subheading] OR ("Drug Toxicity"[Mesh] OR "toxicity "[Subheading]) OR adverse OR harm OR harmful OR safe[tiab] OR safety[tiab] OR toxic*[tiab] AND raloxifene* OR evista OR lasofoxifene* OR selective estrogen receptor modulators OR serm OR serms OR calcium OR "vitamin d" OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR oestrogen OR pth OR parathyroid hormone* OR teriparatide OR forteo OR preos OR alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR

	aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab NOT animal* NOT (human OR humans*) NOT mice OR mouse OR murine OR rat OR rats NOT review[pt]
OR	
9B (Adverse Effects)	osteoporosis OR osteopenia OR osteopaenia OR fracture* OR bone mineral OR fractures[mh] OR bone density AND “adverse effects “[Subheading] OR (“Drug Toxicity”[Mesh] OR “toxicity “[Subheading]) OR adverse OR harm OR harmful OR safe[tiab] OR safety[tiab] OR toxic*[tiab] AND alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab OR bisphosphonate OR bisphosphonates NOT animal* NOT (human OR humans*) NOT mice OR mouse OR murine OR rat OR rats NOT review[pt]
OR	
9C (Adverse Effects)	(osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density AND alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab OR bisphosphonate* OR raloxifene OR lasofoxifene OR serm OR serms OR selective estrogen receptor modulator* OR calcium OR “vitamin d” OR “Estrogens”[Mesh] OR “Estrogens “[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR oestrogen OR pth OR parathyroid hormone* OR teriparatide OR forteo OR preos AND “adverse effects “[Subheading] OR (“Drug Toxicity”[Mesh] OR “toxicity “[Subheading]) OR adverse OR harm OR harmful OR safe[tiab] OR safety[tiab] OR toxic*[tiab] OR risk OR risks OR risking) OR (osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density

	AND raloxifene OR “Estrogens”[Mesh] OR “Estrogens “[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR oestrogen OR (hormone* AND menopaus*) AND thrombosis OR thrombophlebitis OR phlebitis OR clot OR clots OR clotting) OR (alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab OR bisphosphonate* AND esophageal OR esophagus OR fibrillat*) OR (raloxifene AND flash* OR flush*)
N=73742	
Language limit	Filters activated: English
Date Limit	Publication date from 2009/08/01
Journal Limit General Medicine Journals	((((("Annals of internal medicine"[Journal]) OR "BMJ (Clinical research ed.)"[Journal]) OR "JAMA"[Journal]) OR "Lancet (London, England)"[Journal]) OR "The New England journal of medicine"[Journal]
Journal Limit Specialty Journals	(((((("Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA"[Journal])) OR ("Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research"[Journal])) OR ("Current medical research and opinion"[Journal])) OR "Bone"[Journal]) OR ("Journal of bone and mineral metabolism"[Journal])
N=2788	

* Note there were several searches conducted for the review. All of the PubMed searches were re-created and combined in order to reflect the original searches better. The numbering comes from the original document and is not consecutive on order because searches in other databases (EMBASE and International Pharmaceutical Abstracts) were not re-created.

Appendix D. Inclusion and Exclusion Criteria from Original Systematic Review

Populations: Studies were limited to those recruiting the following individuals: adults over 18 (not children); healthy adults, those with low bone density, or those with osteoporosis (but not those with Paget's disease, cancer, or any other disease of bone metabolism); those using drugs indicated for the treatment of osteoporosis (but not if the drugs were being used to treat cancer); adults who had low bone density or were at high risk of developing low bone density as a result of chronic use of glucocorticoids (GC) or a condition associated with the chronic use of glucocorticoids (such as asthma, organ transplant, rheumatoid arthritis; adults who had low bone density or were at high risk of developing low bone density as a result of having a condition associated with low bone density (e.g., rheumatoid arthritis, cystic fibrosis, Parkinson's disease).

Interventions: Studies were included if they examined pharmacological interventions for prevention or treatment of osteoporosis approved for use in the United States (or expected to be soon approved for use) or if they assessed the effects of calcium, vitamin D, or physical activity.

Comparators: Studies included for assessing efficacy or effectiveness were those that compared the effectiveness of the intervention in question to that of placebo or another potency or dosing schedule for the same agent or another agent in the same or another class.

Outcomes: For efficacy and effectiveness analysis, only studies that assessed vertebral, hip, and/or total fractures (and did not state that they lacked power to detect a change in risk for fracture) were included. Studies that reported fracture only as an adverse event were excluded from effectiveness analysis; however, studies that reported atypical (low-stress subtrochanteric or femur) fractures as adverse outcomes were included in the adverse event analysis.

Duration: Studies that had a minimum follow-up time of 6 months were included.

Design: Only RCTs and published systematic reviews of RCTs that met inclusion criteria were included in the assessment of effectiveness; however, for the assessment of effects in subgroups for which no RCTs were available, for the assessment of the effect of adherence on effectiveness, and for the assessment of particular serious adverse events, large observational studies (with more than 1,000 participants) and systematic reviews were included.

Appendix E. Literature Search Results

The literature search identified 2,787 unique titles. Listed below are the 200 randomly selected articles we examined in our assessment of the currency of conclusions in the original systematic review.

1. Aung K. Review: In postmenopausal women and older men, vitamin D plus calcium reduces some fractures. *Annals of internal medicine.* Sep 16 2014;161(6):JC5.
2. Idan A, Griffiths KA, Harwood DT, et al. Long-term effects of dihydrotestosterone treatment on prostate growth in healthy, middle-aged men without prostate disease: a randomized, placebo-controlled trial. *Annals of internal medicine.* Nov 16 2010;153(10):621-632.
3. Nayak S, Roberts MS, Greenspan SL. Cost-effectiveness of different screening strategies for osteoporosis in postmenopausal women. *Annals of internal medicine.* Dec 6 2011;155(11):751-761.
4. Nestle M, Nesheim MC. To supplement or not to supplement: the U.S. Preventive Services Task Force recommendations on calcium and vitamin D. *Annals of internal medicine.* May 7 2013;158(9):701-702.
5. Pregler JP, Crandall CJ. Update in women's health: evidence published in 2010. *Annals of internal medicine.* Jul 5 2011;155(1):52-57.
6. Cutting W. Clear guidance on calcium and vitamin D supplements is lacking. *BMJ (Clinical research ed.).* 2015;351:h5478.
7. Kmietowicz Z. Zoledronic acid increases bone density but does not reduce fractures in frail elderly people, study finds. *BMJ (Clinical research ed.).* 2015;350:h1949.
8. Metcalfe AV, Nordin BE. A reanalysis too far? *BMJ (Clinical research ed.).* 2011;342:d3538.
9. Meyer G, Kopke S. Vitamin D and falls. Information on harm is missing. *BMJ (Clinical research ed.).* 2009;339:b4395.
10. Nordin BE, Daly RM, Horowitz J, Metcalfe AV. Calcium and heart attacks. Making too much of a weak case. *BMJ (Clinical research ed.).* 2010;341:c4997.
11. Paik JM, Curhan GC, Taylor EN. Calcium intake and risk of primary hyperparathyroidism in women: prospective cohort study. *BMJ (Clinical research ed.).* 2012;345:e6390.
12. Sahota O. Reducing the risk of fractures with calcium and vitamin D. *BMJ (Clinical research ed.).* 2010;340:b5492.
13. Vinogradova Y, Coupland C, Hippisley-Cox J. Authors' reply to Abrahamsen and colleagues. *BMJ (Clinical research ed.).* 2013;346:f1518.
14. Wise J. NICE advises certain groups to take daily vitamin D supplement. *BMJ (Clinical research ed.).* 2014;348:g3349.
15. Anastasilakis AD, Polyzos SA, Makras P, et al. Acute phase response following intravenous zoledronate in postmenopausal women with low bone mass. *Bone.* May 2012;50(5):1130-1134.
16. Beck TJ, Fuerst T, Gaither KW, et al. The effects of bazedoxifene on bone structural strength evaluated by hip structure analysis. *Bone.* Aug 2015;77:115-119.
17. Belavy DL, Armbrecht G, Blenk T, et al. Greater association of peak neuromuscular performance with cortical bone geometry, bone mass and bone strength than bone density: A study in 417 older women. *Bone.* Feb 2016;83:119-126.
18. Channon MB, Gordon GW, Morgan JL, Skulan JL, Smith SM, Anbar AD. Using natural, stable calcium isotopes of human blood to detect and monitor changes in bone mineral balance. *Bone.* Aug 2015;77:69-74.
19. Chen F, Wang Z, Bhattacharyya T. Absence of femoral cortical thickening in long-term

bisphosphonate users: implications for atypical femur fractures. *Bone.* May 2014;62:64-66.
20. Chiang CY, Zebaze RM, Ghasem-Zadeh A, Iuliano-Burns S, Hardidge A, Seeman E. Teriparatide improves bone quality and healing of atypical femoral fractures associated with bisphosphonate therapy. *Bone.* Jan 2013;52(1):360-365.
21. Dennison EM, Compston JE, Flahive J, et al. Effect of co-morbidities on fracture risk: findings from the Global Longitudinal Study of Osteoporosis in Women (GLOW). *Bone.* Jun 2012;50(6):1288-1293.
22. Farr JN, Chen Z, Lisse JR, Lohman TG, Going SB. Relationship of total body fat mass to weight-bearing bone volumetric density, geometry, and strength in young girls. *Bone.* Apr 2010;46(4):977-984.
23. Francis SL, Letuchy EM, Levy SM, Janz KF. Sustained effects of physical activity on bone health: Iowa Bone Development Study. *Bone.* Jun 2014;63:95-100.
24. Goodman CA, Hornberger TA, Robling AG. Bone and skeletal muscle: Key players in mechanotransduction and potential overlapping mechanisms. *Bone.* Nov 2015;80:24-36.
25. Grey A, Bolland MJ, Horne A, et al. Five years of anti-resorptive activity after a single dose of zoledronate--results from a randomized double-blind placebo-controlled trial. *Bone.* Jun 2012;50(6):1389-1393.
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27. Imel EA, Eckert G, Modi A, et al. Proportion of osteoporotic women remaining at risk for fracture despite adherence to oral bisphosphonates. *Bone.* Feb 2016;83:267-275.
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32. Madeira E, Mafort TT, Madeira M, et al. Lean mass as a predictor of bone density and microarchitecture in adult obese individuals with metabolic syndrome. *Bone.* Feb 2014;59:89-92.
33. Miyauchi A, Matsumoto T, Sugimoto T, Tsujimoto M, Warner MR, Nakamura T. Effects of teriparatide on bone mineral density and bone turnover markers in Japanese subjects with osteoporosis at high risk of fracture in a 24-month clinical study: 12-month, randomized, placebo-controlled, double-blind and 12-month open-label phases. *Bone.* Sep 2010;47(3):493-502.
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induction chemotherapy for adolescents and young adults treated for acute lymphoblastic leukemia. *Bone.* Apr 2016;85:131-137.
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Appendix F. Questionnaire Sent to Expert Reviewers

AHRQ Systematic Review Surveillance Program

Reviewer Form

Title of Original Systematic Review: Treatment to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis: Update of a 2007 Report

Link to Report

Name of Reviewer: _____

Instructions:

The AHRQ Scientific Resource Center (SRC) periodically conducts surveillance of published AHRQ systematic reviews to assess the currency of review conclusions. The goal of this process is to identify signals that a report may be out of date. One part of this process includes soliciting expert review of our synthesis of recently published literature.

The original systematic review was published in March 2012. The original systematic review search dates covered January 2005-December 2009. We conducted a bridged literature search of select high impact journals from August 2009 to May 2016 and identified evidence potentially related to the key questions of the original systematic review.

The table below highlights the conclusions from the original systematic review and a summary of the relevant recently published literature. No FDA black box warnings were identified. Abstracts from relevant literature are included at the end of the document. If you would like a list of our full search results, please let us know.

Please review the table and provide responses to the questions for each key question below. The primary goal of this review is to identify any important new studies, drugs, interventions, or devices you know of that we may have missed in our literature search and to understand if any new evidence exists which may alter the conclusions of the original systematic review.

Key Question 1:

What are the comparative benefits in fracture risk reduction among the following therapeutic modalities for low bone density:

- Bisphosphonate medications, specifically:
  - Alendronate (Fosamax®, oral)
  - Risedronate (Actonel®; oral once-a-week)
  - Ibandronate (Boniva®)

    - Zoledronic acid (Reclast®IV).
- Denosumab (Prolia®)
- Menopausal estrogen therapy for women (numerous brands and routes of administration)
- Parathyroid hormone (PTH)
    - 1-34 (teriparatide) (Forteo®)
- Selective estrogen receptor modulators (SERMs), specifically:
    - Raloxifene (Evista®)
- Calcium
- Vitamin D
- Combinations or sequential use of above
- Exercise in comparison to above agents

Current Literature Analysis:

- We identified one large RCT (n=7,808) comparing subcutaneous injections of 60 mg of denosumab to placebo every six months for three years in postmenopausal women with osteoporosis. Results indicated that the treatment group had fewer vertebral, non-vertebral, and hip fractures.[1]
- We identified one RCT of postmenopausal women with spinal osteoporosis and back pain (n=59) and the effects of various exercise programs on fracture incidence. Results suggest that a significantly higher number of vertebral compression fractures occur in patients with postmenopausal osteoporosis who followed a flexion exercise program compared with those using extension exercises. Extension or isometric exercises seem to be more appropriate for patients with postmenopausal osteoporosis.[2]
- A partially randomized comprehensive cohort study lasting 10 years (n=2016) examined premenopausal women compared the effect of NSAIDs, paracetamol, opioids, or acetylsalicylic acid on fracture incidence. After adjusting for relevant confounding variables, individuals receiving NSAIDs sustained more fractures than comparators and paracetamol and opioids were associated with a non-significant trend towards more fractures. No excess risk of fractures was associated with ASA.[3]

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 2:

How does fracture risk reduction resulting from treatments vary between individuals with different risks for fracture as determined by the following factors:

- Bone mineral density
- FRAX or other risk assessment score
- Prior fractures (prevention vs. treatment)
- Age
- Sex
- Race/ethnicity
- Glucocorticoid use

- Other factors (e.g., whether the individuals were community dwelling vs. institutionalized, vitamin D deficient vs. not)

Current Literature Analysis:

- One RCT noted that denosumab recently received regulatory approval for the treatment of postmenopausal women with osteoporosis at high risk for fracture, with no dose adjustment in patients with renal impairment.[1] The same RCT found that, in high fall risk populations, the denosumab group had fewer incidences of falling and concussions.[1]

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

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2. Are there any published or unpublished studies that you know of that we may have overlooked?

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Key Question 3:

Regarding treatment adherence and persistence,

- What are the levels of adherence to and persistence with medications for the treatment and prevention of osteoporosis?
- What factors affect adherence and persistence?

Current Literature Analysis:

- No new studies were identified.

Reviewer Questions:

3. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

4. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 4:

What are the short- and long-term harms (adverse effects) of the above therapies (when used specifically to treat or prevent low bone density/osteoporotic fracture), and do these vary by any specific subpopulations (e.g., the subpopulations identified in Key Question 2)?

Current Literature Analysis:

- A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. The following adverse events were reported: cerebrovascular accident, myocardial infarction, gastrointestinal events, headaches/dizziness, death, transient ischemic attack, arrhythmia, dyspnea, and hypertension.[4]
- A double-blind RCT (n=143) compared the use of raloxifene at 60 mg/day or 120 mg/day to a control group receiving supplements of calcium (750 mg/day) and vitamin D (400 IU/day) in postmenopausal osteoporotic women (mean age=68.4). The following adverse events were reported: arthralgia, dizziness in non-hypotensive populations, and hypotension.[5]

- In a three-year, randomized, placebo-controlled clinical trial in postmenopausal women with osteoporosis (n=7,808), patients who were treated with 60 mg of denosumab (vs placebo) every six months for three years had fewer incidences of eczema, cellulitis, falling, and concussions.[1]

Reviewer Questions:

5. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

6. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 5:

With regard to treatment for preventing osteoporotic fracture:

a. How often should patients be monitored (via measurement of bone mineral density) during therapy, how does bone density monitoring predict antifracture benefits during pharmacotherapy, and does the ability of monitoring to predict antifracture effects of a particular pharmacologic agent vary among the pharmacotherapies?
b. How does the antifracture benefit vary with long-term continued use of pharmacotherapy, and what are the comparative antifracture effects of continued long-term therapy with the various pharmacotherapies?

Current Literature Analysis:

- No new studies were identified for key question 5a or 5b.

Reviewer Questions:

7. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

8. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Original Systematic Review Conclusions and Literature Analysis

Title of Original Systematic Review: Treatment to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis: Update of a 2007 Report
Original Systematic Review Published: March 2012
Original Systematic Review Search Dates: January 2005 to December 2009
Current Literature Search Dates: August 2009-May 2016

The conclusions from the original systematic review and a summary of the relevant recently published literature. No FDA black box warnings/Class I recalls as applicable to the report were identified. Abstracts are provided at the end of the document.

Table 1. Key Question 1: What are the comparative benefits in fracture risk reduction among the following treatments for low bone density?

Conclusions From Original Systematic Review **Link to Report**	**Literature Analysis (May 2016)**
Bisphosphonates: Vertebral Fractures **SOE: High** In two pooled analyses (two RCTs) of alendronate vs placebo, the treatment group has been shown to reduce the risk of vertebral fractures among postmenopausal women with osteoporosis. In two pooled analyses (three RCTs) of risedronate vs placebo, the treatment group has been shown to reduce the risk of vertebral fractures among postmenopausal women with osteoporosis at a dose of 5.0 mg (decreased risk of 58% [1 RCT]), and does not significantly reduce the risk of vertebral fractures at 35 mg per week (3 RCTs). No studies evaluating 2.5 mg per day or 30 mg per week were found. In one pooled analysis (one RCT) of ibandronate vs placebo, the treatment group has been shown to reduce the risk of vertebral fractures among postmenopausal women with osteoporosis. In two RCTs of zoledronic acid vs placebo, the treatment group has been shown to reduce the risk of vertebral fractures among postmenopausal women with osteoporosis at a dose of 5.0 mg (one time only [one RCT]) and 2.0 mg (every six months [one RCT]). No studies evaluating 4.0 mg (one time only), 1 mg (every three months), 0.5 mg (every three months), or 0.25 mg (every three months) were	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
found.	
Bisphosphonates: Non-Vertebral Fractures **SOE: High** In one pooled analysis (two RCTs) of alendronate vs placebo, the treatment group has been shown to reduce the risk of non-vertebral fractures among postmenopausal women with osteoporosis. In two pooled analyses (four RCTs) of risedronate vs placebo, the treatment group has been shown to reduce the risk of nonvertebral fractures among postmenopausal women with osteoporosis at a dose of 2.5 mg per day (decreased risk of 71% [1 RCT]) and 35 mg per week (two RCTs). While a dose of 5.0 mg per day in men at 12 months does not significantly reduce fractures (two RCTs), a dose of 5.0 mg per day at 24 month does significantly reduce the risk of nonvertebral fractures in men. No studies evaluating 30 mg per week were found. In two pooled analysis (no new RCTs) of ibandronate vs placebo, the treatment group has been shown to reduce the risk of non-vertebral fractures among postmenopausal women with osteoporosis. In two RCTs of zoledronic acid vs placebo, the treatment group has been shown to reduce the risk of nonvertebral fractures among postmenopausal women with osteoporosis at a dose of 5.0 mg (one time only [one RCT]) and 2.0 mg (every six months [one RCT]). No studies evaluating 4.0 mg (one time only), 1 mg (every three months), 0.5 mg (every three months), or 0.25 mg (every three months) were found.	No studies were identified.
Bisphosphonates: Hip Fractures **SOE: High** In one pooled analysis (no new RCTs) of alendronate vs placebo, the treatment group has been shown to reduce the risk of hip fractures among postmenopausal women with osteoporosis by 70%. In one pooled analysis (three RCTs) of risedronate vs placebo, the treatment group has been shown to reduce the risk of hip fractures among postmenopausal women with osteoporosis at a dose of 2.5 mg	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
per day (decreased risk of 71% [three RCT]). No studies evaluating 5.0 mg per day, 30 mg per week, or 35 mg per week were found. No studies of hip risk fracture in ibandronate vs placebo were found. In one RCT of zoledronic acid vs placebo, the treatment group has been shown to reduce the risk of hip fractures among postmenopausal women with osteoporosis at a dose of 5.0 mg (one time only [one RCT]). No studies evaluating 4.0 mg (one time only), 2.0 mg (every six months), 1 mg (every three months), 0.5 mg (every three months), or 0.25 mg (every three months) were found.	
Bisphosphonates: Wrist Fractures **SOE: Low** In one pooled analysis (no new RCTs) of alendronate vs placebo, the treatment group has been shown to not reduce the risk of wrist fractures among postmenopausal women with osteoporosis. In one pooled analysis (one RCT) of risedronate vs placebo, the treatment group has been shown to not reduce the risk of wrist fractures among postmenopausal women with osteoporosis at a dose of 5.0 mg per day. No studies evaluating 2.5 mg per day, 30 mg per week, or 35 mg per week were found. No studies of wrist risk fracture in ibandronate vs placebo were found. No studies of wrist risk fracture in zoledronic acid vs placebo were found.	No studies were identified.
SERMs (raloxifene): Vertebral Fractures **SOE: High** Raloxifene reduces the risk of vertebral fractures (two RCTs) among postmenopausal women with osteoporosis.	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
SERMs (raloxifene): Non-Vertebral Fractures **SOE: High** Raloxifene does not reduce the risk of nonvertebral fractures (two RCTs) among postmenopausal women with osteoporosis.	No studies were identified.
SERMs (raloxifene): Hip Fractures **SOE: High** Raloxifene does not reduce the risk hip fractures (one RCT) among postmenopausal women with osteoporosis.	No studies were identified.
SERMs (raloxifene): Wrist Fractures **SOE: High** Raloxifene does not reduce the risk of wrist fractures (one RCT) among postmenopausal women with osteoporosis.	No studies were identified.
PTH (teriparatide): Vertebral Fractures **SOE: High** In the RCT with the fewest number of vertebral fracture events, vertebral fracture risk was no different with teriparatide than placebo; however, the remainder of the RCTs demonstrated vertebral fracture risk to be statistically significantly lower with teriparatide than with placebo.	No studies were identified.
PTH (teriparatide): Non-Vertebral Fractures **SOE: High** In one pooled analysis (5 RCTs) of teriparatide vs placebo, the treatment group has been shown to reduce the risk of non-vertebral fractures among postmenopausal women with osteoporosis.	No studies were identified.
PTH (teriparatide): Hip Fractures No studies of hip risk fracture in teriparatide vs placebo were found.	No studies were identified.
PTH (teriparatide): Wrist Fractures No studies of wrist risk fracture in teriparatide vs placebo were found.	No studies were identified.
Menopausal Hormone Therapy: Vertebral Fractures **SOE: High**	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
Menopausal hormone therapy does not statistically significantly reduce the risk of vertebral fractures in postmenopausal women (one trial).	
Menopausal Hormone Therapy: Non-Vertebral Fractures **SOE: High** Menopausal hormone therapy does not statistically significantly reduce the risk of nonvertebral fractures in postmenopausal women (one trial).	No studies were identified.
Menopausal Hormone Therapy: Hip Fractures No studies of risk of hip fracture in menopausal hormone therapy vs placebo were found.	No studies were identified.
Menopausal Hormone Therapy: Wrist Fractures No studies of risk of wrist fracture in menopausal hormone therapy vs placebo were found.	No studies were identified.
Denosumab: Vertebral Fractures **SOE: High** In two RCTs of denosumab vs placebo, the treatment group has been shown to reduce the risk of vertebral fractures among postmenopausal women with osteoporosis.	In a three-year, randomized, placebo-controlled clinical trial in postmenopausal women with osteoporosis (n=7,808), patients who were treated with 60 mg of denosumab (vs placebo) every six months for three years had fewer vertebral fractures.[1]
Denosumab: Non-Vertebral Fractures **SOE: High** In two RCTs of denosumab vs placebo, the treatment group has been shown to reduce the risk of vertebral fractures among postmenopausal women with osteoporosis.	In a three-year, randomized, placebo-controlled clinical trial in postmenopausal women with osteoporosis (n=7,808), patients who were treated with 60 mg of denosumab (vs placebo) every six months for three years had fewer non-vertebral fractures.[1]
Denosumab: Hip Fractures **SOE: High** In one RCT of denosumab vs placebo, the treatment group has been shown to reduce the risk of hip fractures among postmenopausal women with osteoporosis.	In a three-year, randomized, placebo-controlled clinical trial in postmenopausal women with osteoporosis (n=7,808), patients who were treated with 60 mg of denosumab (vs placebo) every six months for three years had fewer hip fractures.[1]
Denosumab: Wrist Fractures No studies of wrist risk fracture in denosumab vs placebo were found.	No studies were identified.
Denosumab: Other Fractures	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
In one meta-analysis (three RCTs) of denosumab vs placebo, the treatment group has been shown to reduce the risk of all fracture types among postmenopausal women with osteoporosis. In one pooled analysis of denosumab vs placebo, the treatment group has been shown to reduce the risk of clinical fractures among postmenopausal women with osteoporosis.	
Calcium: Vertebral Fractures **SOE: Moderate** Two RCTs showed the risk of vertebral fractures to be not statistically different with calcium compared to placebo.	No studies were identified.
Calcium: Non-Vertebral Fractures **SOE: Moderate** Two RCTs showed the risk of non-vertebral fractures to be not statistically different with calcium compared to placebo.	No studies were identified.
Calcium: Hip Fractures **SOE: Moderate** One pooled estimate showed a 64% increase in risk of hip fracture associated with calcium supplementation. However, another pooled estimate of a meta-analysis with almost ten times more participants found a 25% reduction in risk of hip fracture with calcium compared to a placebo. Therefore, data on the effects of calcium supplementation on hip fractures is conflicting.	No studies were identified.
Calcium: Wrist Fractures **SOE: Moderate** Two RCTs showed the risk of wrist fractures to be not statistically different with calcium compared to placebo.	No studies were identified.
Calcium: All Fractures **SOE: Moderate** In one systematic review of 16 RCTs of calcium vs placebo, the treatment group has been shown to reduce the risk of all fractures among postmenopausal women with osteoporosis. One new RCT was	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
identified.	
Vitamin D: Vertebral Fractures **SOE: Low-Moderate** In a pooled analysis of vitamin D vs placebo, the treatment group has been shown to reduce the risk of vertebral fractures among postmenopausal women with primary osteoporosis, but was not associated with a reduction in vertebral fracture risk in those with prior fractures, women with severe osteoporosis, or those taking glucocorticoid treatment. Of note, results are inconsistent across pooled analyses. Four new RCTs were identified.	No studies were identified.
Vitamin D: Nonvertebral Fractures **SOE: Low-Moderate** In a meta-analysis of vitamin D vs placebo, the treatment group has been shown to reduce the risk of nonvertebral fractures among elderly women not selected for prior osteoporotic fracture, vitamin D analogues (alfacalcidol and calcitriol) for primary osteoporosis, and standard vitamin D for primary osteoporosis. In contrast, two systematic reviews report that the following were not associated with statistically significant reductions in nonvertebral fracture risk: alfacalcidol, calcitriol, or vitamin D among people not selected on the basis of prior osteoporotic fracture, calcitriol among women with severe osteoporosis. Six new RCTs were identified.	No studies were identified.
Vitamin D: Hip Fractures **SOE: Low-Moderate** For hip fracture, compared to placebo, alfacalcidol (vitamin D analogue) reduced relative risk of fracture by 84% (on systematic review). Both standard vitamin D and calcitriol (vitamin D analogue) were not statistically significantly more effective than placebo in reducing hip fracture risk among those who were not selected, nor among those who were selected, on the basis of previous osteoporotic fractures. One pooled estimate showed a statistically significantly increased risk of hip	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
fracture in associated with injection of vitamin D compared to placebo. Seven new RCTs were identified.	
Vitamin D: Wrist Fractures **SOE: Insufficient** No studies of risk of wrist fracture in vitamin D vs placebo were found.	No studies were identified.
Vitamin D: All Fractures **SOE: Low-Moderate** The effect of vitamin D on fracture risk is uncertain. Among a number of meta-analyses, some reported a reduced risk for vitamin D relative to placebo, some did not. There was no reduction in fracture risk for vitamin D relative to placebo in a large, high quality RCT published after the meta-analyses.	No studies were identified.
Vitamin D + Calcium: Vertebral Fractures **SOE: Low-Moderate** When compared to placebo, vitamin D + calcium was not associated with statistically significant reductions in vertebral fractures.	No studies were identified.
Vitamin D + Calcium: Nonvertebral Fractures **SOE: Low-Moderate** In combination with calcium, vitamin D was associated with a statistically significant reduction in nonvertebral fracture risk among populations not selected on the basis of prior osteoporotic fractures in two systematic reviews. Standard vitamin D doses of ≥700 IU/d + calcium are associated with statistically significant reductions in nonvertebral fracture risk among institutionalized persons. A third systematic review shows, among institutionalized persons, vitamin D + calcium was associated with a 15% decrease (statistically significant) in nonvertebral fracture risk. The same review reported that vitamin D + calcium was not associated with a statistically significantly decreased risk of nonvertebral fractures among those who were not selected on the basis of prior osteoporotic fractures, those who were selected on the basis of prior osteoporotic fractures, or among	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
community-dwellers.	
Vitamin D + Calcium: Hip Fractures **SOE: Low-Moderate** Vitamin D + calcium (vs. placebo) was associated with statistically significantly reduced risk of hip fracture, ranging about 20% to 30%, in those selected or not selected on the basis of prior osteoporotic fractures (in some studies), not selected on the basis of low BMD, and among the institutionalized. Vitamin D + calcium did not decrease hip fracture risk more than placebo among community dwellers and general populations, even at high (≥700 IU/d) doses. Vitamin D doses of 10 µg were not effective in decreasing hip fracture risk unless they were given with calcium. Dosing of ≥700 IU of vitamin D was associated with a 28 percent lower risk of hip fractures among institutionalized persons. A new systematic review found that vitamin D supplementation did not statistically significantly alter hip fracture risk, but the authors analyzed vitamin D plus calcium and vitamin D jointly, in comparison to a reference group of placebo or calcium, respectively.	No studies were identified.
Vitamin D + Calcium: Wrist Fractures **SOE: Insufficient** No studies of risk of wrist fracture in vitamin D + calcium vs placebo were found.	No studies were identified.
Exercise vs above agents **SOE: Insufficient** There are no data from RCTs to inform this question. One RCT that assessed the effect of a brief exercise program on fracture risk found a small decrease in risk of fractures among exercisers but the study was not powered to detect differences in fracture risk.	A RCT of 59 postmenopausal women with spinal osteoporosis and back pain (ages ranging from 49-60; mean=56) suggests that a significantly higher number of vertebral compression fractures occur in patients with postmenopausal osteoporosis who followed a flexion exercise program compared with those using extension exercises. Extension or isometric exercises seem to be more appropriate for patients with postmenopausal osteoporosis.[2]

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
Head-to-Head Comparisons **SOE: Insufficient** No new studies were identified for the following head-to-head comparisons: • Menopausal estrogen therapy vs bisphosphonate therapy • Bisphosphonate therapy vs calcium • Bisphosphonate therapy vs raloxifene • Alendronate vs risedronate in women with osteoporosis • Alendronate vs raloxifene among postmenopausal • Risedronate vs zoledronic acid • Etidronate vs calcitonin • Raloxifene vs menopausal estrogen therapy • Calcium vs Vitamin (or Vitamin D vs Calcium)	No studies were identified.
Head-to-Head Comparisons • **Alendronate 10 mg/day vs teriparatide 20 µg/day** SOE: High In one 36-month RCT of people taking glucocorticoids, the odds of vertebral fracture and the risk of nonvertebral fracture were similar with alendronate 10 mg/day vs teriparatide 20 µg/day. • **Alendronate + Vitamin D vs Alendronate + Alfacalcidol** SOE: High In one 24-month RCT, the odds of vertebral fracture were higher and the risk of nonvertebral fracture was similar with alendronate + vitamin D vs alendronate + alfacalcidol. • **Alfacalcidol + Prednisone + Alendronate vs Alfacalcidol + Prednisone** SOE: Low One RCT reported 90% lower odds of vertebral fracture with alfacalcidol + prednisone + alendronate vs alfacalcidol + prednisone. • **Alendronate vs. Alendronate + Calcium** SOE: Moderately High A RCT found three-fold higher odds of any of any clinical fracture with alendronate vs alendronate + calcium. • **Rocaltrol + Caltrate D vs Caltrate D** SOE: Moderately High	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
A 12-month RCT found that rocaltrol + Caltrate D did not statistically significantly decrease the odds of vertebral fracture compared to Caltrate D. • **Menopausal Estrogen Therapy vs Vitamin D** SOE: Low One RCT examined vertebral and nonvertebral fractures in aggregate found that the odds of fracture were not statistically significantly different with menopausal estrogen +progestogen therapy vs vitamin D.	
Paracetamol, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Acetylsalicylic Acid (ASA), and Opioids: All Fractures **SOE: Not Reported** RCTs that directly compared paracetamol, NSAIDs, ASA, and opioids on fractures were not included in the original review.	A partially randomized comprehensive cohort study lasting 10 years (n=2016) examined premenopausal women compared the effect of NSAIDs, paracetamol, opioids, or acetylsalicylic acid on fracture incidence. After adjusting for relevant confounding variables, individuals receiving NSAIDs sustained more fractures than comparators and paracetamol and opioids were associated with a non-significant trend towards more fractures. No excess risk of fractures was associated with ASA.[3]

Abbreviations: RCT=Randomized Controlled Trial; SOE=Strength of Evidence

Table 2. Key Question 2: How does fracture risk reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density (borderline/low/severe), risk assessment score, prior fractures (prevention vs. treatment), age, sex, race/ethnicity, and glucocorticoid use?

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
Fracture Risk Reduction: Bone Mineral Density **SOE: Moderate** A post hoc analysis of FIT/FLEX in postmenopausal women with low femoral neck BMD who had initially completed five years of alendronate therapy were assigned to receive another five years of therapy or five years of placebo. Both treatment arms received calcium and vitamin D. Incidence of nonvertebral and clinical fractures did not significantly differ among women who had lower baseline BMD vs women who had higher baseline BMD. A post hoc analysis of risedronate efficacy was performed among women with femoral T-score between -1 and -2.5 without prevalent fracture (osteopenia). Cumulative 2-year fragility fracture incidence was	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
statistically significantly lower among women assigned to risedronate compared to placebo, and comparable to reductions seen in women with osteoporosis. No trials that included stratified analyses of fracture risk reduction based on bone mineral density while being treated with ibandronate, zoledronic acid, teriparatide, raloxifene, hormone replacement therapy, denosumab, vitamin D, or calcium were found.	
Fracture Risk Reduction: FRAX or Other Assessment Scores **SOE: Moderate** A post hoc analysis of the MORE raloxifene trial failed to show significant differences in the risk of overall fracture and of incident morphometric vertebral fractures associated with raloxifene vs placebo according to the FRAX score. The post hoc analysis of raloxifene vs placebo did, however, show a 31% decrease in fractures in those 75 years or older, irrespective of FRAX score. At younger ages, effectiveness of raloxifene increased (decreased fracture risk). Additionally, raloxifene prevents fractures in postmenopausal women at low risk for fracture, as assessed by FRAX. No trials that included stratified analyses of fracture risk reduction using FRAX and other assessment scores while being treated with bisphosphonates, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium were found.	No studies were identified.
Fracture Risk Reduction: Prior Fractures (Prevention vs Treatment) **SOE: Moderate-Low** A post hoc analysis of FIT/FLEX in postmenopausal women with low femoral neck BMD who had initially completed five years of alendronate therapy were assigned to receive another five years of therapy or five years of placebo. Both treatment arms received calcium and vitamin D. Cumulative incidence of nonvertebral and clinical vertebral fractures did not significantly differ among women who had prevalent vertebral fractures at baseline. In a post hoc analysis of the FIT trial with the same 5-year extension as	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
the previously described study, among women with prevalent vertebral fracture at baseline, continued alendronate reduced the risk of clinical (but not morphometric) vertebral fractures, but not morphometric or nonvertebral fractures. In contrast, among women without vertebral fractures at baseline, alendronate continuation reduced nonvertebral fractures among women with baseline femoral neck T-score ≤-2.5, but not with T-score between -2 and -2.5. An extension of the MORE trial of raloxifene examined the relative efficacy of raloxifene among women with, compared to without, prevalent vertebral fractures. Although raloxifene did not statistically significantly influence nonvertebral fracture risk, raloxifene did decrease the risk of major nonvertebral fracture (clavicle, humerus, wrist, pelvis, hip, lower leg) among women with prevalent vertebral fracture, but not among women without prevalent vertebral fracture at baseline. A post hoc analysis examined the effects of raloxifene on new vertebral fractures according to the presence or absence of prevalent fractures. The efficacy of raloxifene compared to placebo on decreasing vertebral fractures did not differ statistically significantly between women with and without prevalent fractures, (-8.21%, -0.75% vs. -2.83%, -1.21%, respectively). Among postmenopausal women with osteoporosis who were randomized to teriparatide therapy in the Fracture Prevention Trial, the absolute benefit of teriparatide was greater among women with the highest number and severity of prevalent vertebral fractures. No trials that included stratified analyses of fracture risk reduction by prior fractures while being treated with ibandronate, risedronate, zoledronic acid, hormone replacement therapy, denosumab, vitamin D, or calcium were found.	
Fracture Risk Reduction: Age **SOE: High** A post hoc analysis examined the relationship between age and the effect of risedronate treatment on fracture risk among postmenopausal women with osteoporosis. Irrespective of age, when compared to	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
placebo, risedronate decreased the risk for any fracture, clinical fracture, nonvertebral fracture, and morphometric vertebral fracture statistically significantly. In a post hoc analysis of postmenopausal women with osteoporosis, zoledronic acid significantly reduced clinical fractures, clinical vertebral fractures, and non-vertebral fractures across age groups (younger than 75 years old and equal to or older than 75 years old). However, only women younger than 75 had statistically significant reduction in hip fracture risk at three years. In a post hoc analysis of the HORIZON trial, zoledronic acid was reported to reduce vertebral fracture risk statistically significantly among women < 70 years old. However, no such treatment-age interaction was apparent for nonvertebral or hip fractures. In a post hoc analysis of the MORE raloxifene trial, antifracture effects of raloxifene vs. placebo were higher at younger ages. In a post hoc analysis of the Fracture Prevention Trial of postmenopausal women with osteoporosis, the relative risk of new vertebral fracture associated with teriparatide vs. placebo was similar among age subgroups. Risk of vertebral fracture among both women under 75 years and women 75 and over was statistically significant. For nonvertebral fractures the risk of fracture among women under 75 years was statistically significant, but not for women 75 years and over. However, treatment by age interactions was not statistically significant. Compared to placebo, annual intramuscular injection of vitamin D2 (ergocalciferol) 300,000 IU for 3 years among men and women aged 75 years and over did not reduce the risk of any first fracture, or wrist fracture, and it increased the risk of hip fracture. Associations of vitamin D2 with fracture risk did not vary according to sex, age, previous fracture, or mobility. No trials that included stratified analyses of fracture risk reduction by age while being treated with alendronate, ibandronate, hormone replacement therapy, denosumab, or calcium were found.	

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
Fracture Risk Reduction: Sex **SOE: Insufficient** Two trials of vitamin D reported fracture outcomes and included a sufficient number of men. A factorial cluster-randomized intervention study administered calcium carbonate and vitamin D3 (400 IU) tic immunity dwelling residents aged 66+. While fracture risk was statistically significantly reduced in women, fracture risk was not statistically significantly reduced in male participants, possibly because fractures were relatively rare in elderly men. In the second trial, 9,440 men and women over the age of 75 living in Wales were randomized to receive 300,000 IU of ergocalciferol by IM injection. There was no statistically significant reduction in overall or site-specific fracture. Of note, women had an increased risk of wrist fracture in the vitamin D treatment group, while no significant differences were seen in men. While there are no published trials assessing the antifracture effects of any of the aforementioned agents (bisphosphonates, raloxifene, teriparatide, hormone replacement therapy, denosumab, or calcium) in men that are comparable to the large, international, placebo controlled trials that exist for women, nine trials that enrolled either all male subjects or had greater than 50% male subjects enrolled were found. However, these trials were either about special populations, were not powered to detect fracture risk outcomes, or were open-label.	No studies were identified.
Fracture Risk Reduction: Race/Ethnicity **SOE: High** A post hoc analysis of the HORIZON trial in 323 Chinese women from Taiwan and Hong Kong found that once-yearly zoledronic acid was associated with a significant 52% reduction in morphometric vertebral fracture at three years. A pooled analysis of two studies of Asian postmenopausal women with osteoporosis (one Chinese and one Japanese) examined the effects of raloxifene (60 mg/d or 120 mg/d vs. placebo). Raloxifene statistically significantly reduced the incidence of vertebral fractures and any new clinical fractures, but not nonvertebral fractures, compared to placebo.	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
No trials that included stratified analyses of fracture risk reduction by age while being treated with alendronate, ibandronate, risedronate, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium were found.	
Fracture Risk Reduction: Glucocorticoid Use **SOE: Moderate-High** As reported in a 36-month RCT of people taking glucocorticoids, the odds of vertebral fracture were higher, and the risk of nonvertebral fracture was similar, with alendronate 10 mg/day vs. teriparatide 20 µg/day. A RCT newly identified for this report that examined vertebral and nonvertebral fractures in aggregate found that the odds of fracture were not significantly different with menopausal estrogen + progestogen therapy vs. vitamin D. No trials that included stratified analyses of fracture risk reduction by glucocorticoid use while being treated with bisphosphonates, raloxifene, denosumab, or calcium were found.	No studies were identified.
Fracture Risk Reduction: Renal Function **SOE: Insufficient** In a subgroup analysis of the FIT alendronate trial of women with osteoporosis, alendronate reduced the risk of spine fractures and overall clinical fractures to a similar extent to those without reduced renal function. In a post hoc analysis of the HORIZON trial, antifracture effects of zoledronic acid were evaluated in relation to subgroups defined by age, body mass index, and renal function. The effects of zoledronic acid on reducing vertebral fracture risk were statistically significantly greater among women who were overweight or obese, and those who had creatinine clearance >60 ml/minute. However, no such treatment-factor interactions were apparent for nonvertebral or hip fractures. A post hoc analysis from the MORE raloxifene trial showed that irrespective of kidney function (creatinine clearance level at baseline), raloxifene treatment was associated with a reduction in vertebral	Denosumab recently received regulatory approval for the treatment of postmenopausal women with osteoporosis at high risk for fracture, with no dose adjustment in patients with renal impairment.[1]

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
fractures, and no effect on nonvertebral fractures, compared to placebo. In a post-hoc analysis, a lower incidence of vertebral and nonvertebral fractures in teriparatide-treated versus placebo-treated patients was statistically consistent among patients with normal and impaired renal function. No trials that included stratified analyses of fracture risk reduction by renal function while being treated with ibandronate, risedronate, hormone replacement therapy, denosumab, vitamin D, or calcium were found.	
Fracture Risk Reduction: Timing of Initiation of Treatment **SOE: Low** A post hoc study focused on the timing of administration of zoledronic acid among men and women in the first 90 days after surgical hip fracture repair. Clinical fracture reduction was statistically significant, and was not significantly different among participants who had initiated zoledronic acid within 6 weeks (33%) compared with after 6 weeks (37%). No trials that included stratified analyses of fracture risk reduction by timing of initiation of treatment while being treated with alendronate, ibandronate, risedronate, raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium were found.	No studies were identified.
Fracture Risk Reduction: Cystic Fibrosis **SOE: Insufficient** A systematic review that included five trials of persons with cystic fibrosis (CF) who had not undergone lung transplants assessed the efficacy of bisphosphonates for fracture prevention in this group. Bisphosphonates increased BMD but had no significant effect on incident fracture in this population, a finding attributed, at least in part, to the small sample size and short duration of follow-up. No trials that included stratified analyses of fracture risk reduction by timing of initiation of treatment while being treated with raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
calcium were found.	
Fracture Risk Reduction: High Risk Groups (including women with osteoporosis, transplant recipients, and high fall-risk populations) **SOE: High-Moderate** Reduction in fracture risk for subjects treated with alendronate, risedronate, or vitamin D has been demonstrated in populations at increased risk for fracture due to conditions that increase the risk of falling including stroke with hemiplegia, Alzheimer's disease, and Parkinson's. There are limited and inconclusive data on the effect of agents for the prevention and treatment of osteoporosis on transplant recipients and patients treated with chronic corticosteroids. Alendronate, ibandronate, risedronate, teriparatide, raloxifene, zoledronic acid, and denosumab reduce the risk of fractures among high risk groups including postmenopausal women with osteoporosis.	In a three-year, randomized, placebo-controlled clinical trial in postmenopausal women with osteoporosis (n=7,808), patients who were treated with 60 mg of denosumab (vs placebo) every six months for three years had fewer incidences of falling and concussions.[1]

Abbreviations: BMD=Bone Mineral Density; FRAX=Fracture Risk Assessment Tool; SOE=Strength of Evidence

Table 3. Key Question 3: What are the adherence and persistence with medications for the treatment and prevention of osteoporosis, the factors that affect adherence and persistence, and the effects of adherence and persistence on the risk of fractures?

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
Adherence and Persistence to Therapy **SOE: Moderate-High** Eighteen RCTs reported rates of adherence to therapy. Twelve trials with bisphosphonates (five with alendronate, five with risedronate, and two with ibandronate) and two trials with denosumab reported high levels of adherence (majority with over 90% adherence). Two trials with raloxifene had adherence rates 65-70%. There is evidence from 58 observational studies, including 24 using U.S. data, that adherence and persistence with therapy with bisphosphonates, calcium, and vitamin D is poor in many patients with osteoporosis. One study described adherence with teriparatide. No studies describe primary nonadherence (i.e. nonfulfillment).	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
It is important to note that adherence rates are higher in clinical trials than in real life and therefore in observational studies, which likely reflects the select populations and controlled environments in trials.	
Factors Affecting Adherence **SOE: Moderate-High** Based on evidence from 41 observational studies, many factors affect adherence and persistence with medications including, but not limited to: • Dosing frequency: Based on 20 observational studies, dosing frequency appears to affect adherence/persistence. Adherence is improved with weekly compared to daily regimens, but current evidence is lacking to show that monthly regimens improve adherence over that of weekly regimens; • Side effects of medications: Nine studies reported a significant effect of medication-associated adverse events on adherence or persistence, especially bisphosphonates (evidence from a systematic review and 15 out of 17 observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, nonvertebral or both); • Co-morbid conditions • Knowledge about osteoporosis • Cost Age, prior history of fracture, and concomitant medication use do not appear to have an independent association with adherence or persistence. The evidence on adherence to raloxifene, teriparatide, and other drugs and its association with fracture risk is insufficient to make conclusions.	No studies were identified.
Association Between Adherence and Fracture Risk **SOE: Low** The evidence on adherence to raloxifene, teriparatide, and other drugs and its association with fracture risk is insufficient to make conclusions.	No studies were identified.

Abbreviations: RCT=Randomized Controlled Trial; SOE=Strength of Evidence; U.S.=United States

Table 4. Key Question 4: What are the short- and long-term harms (adverse effects) of the above therapies, and do these vary by any specific subpopulations?

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
Risk of PE **SOE: High** One RCT comparing risedronate vs placebo found no significant differences in risk for PE. Two RCTs show participants who took raloxifene were at higher odds for PE than did participants who took a placebo. No RCTs of alendronate, ibandronate, zoledronic acid, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting risk of PE were found.	No studies were identified.
Risk of TE Events **SOE: High** One RCT comparing alendronate vs placebo found no significant differences in risk for TE. Four RCTs examining raloxifene vs placebo were examined. Individuals in the treatment group showed higher odds for venous TE. Estrogen and estrogen-progestin combination participants had higher odds of thromboembolic events than did placebo participants. No RCTs of ibandronate, risedronate, zoledronic acid, teriparatide, denosumab, vitamin D, or calcium reporting risk of TE were found.	No studies were identified.
Risk of Cerebrovascular Accident (CeVA) **SOE: High** Three RCTs of raloxifene reporting CeVA were evaluated. A pooled analysis showed no significant risk for CeVA in the treatment groups. Estrogen and estrogen-progestin combination participants had higher odds of cerebrovascular accident (CeVA) than did placebo participants.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 2.5% of the 351 adverse events reported (approximately 9 reports) were cerebrovascular accidents.[4]

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
One placebo-controlled trial of calcium found an increase in CeVA among users. No RCTs of bisphosphonates, teriparatide, denosumab, or vitamin D reporting risk of CeVA were found.	
Risk of Serious Cardiovascular Events **SOE: Not Reported** A pooled analysis of 16 trials showed a small but significant increase in serious cardiovascular adverse effects for raloxifene compared to placebo. No RCTs of bisphosphonates, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting serious cardiovascular events (not death) were found.	No studies were identified.
Risk of Acute Coronary Syndrome **SOE: Moderate** Three RCTs comparing raloxifene vs placebo found no significant differences in risk of acute coronary syndrome. No RCTs bisphosphonates, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting acute coronary syndrome were found.	No studies were identified.
Risk of Atrial Fibrillation **SOE: Insufficient** One RCT found no significant difference in risk for atrial fibrillation in individuals treated with raloxifene vs placebo. No RCTs of bisphosphonates, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting atrial fibrillation were found.	No studies were identified.
Risk of Myocardial Infarction **SOE: Low** A meta-analysis of 15 placebo-controlled trials of calcium identified a	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 2.5% of the 351 adverse events reports (approximately 9 reports) were myocardial infarctions.[4]

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
small but significant increase in the risk for myocardial infarction in pooled results of five trials that contributed patient-level data. Trial – level data showed a similar effect. However, professional and clinical response to this meta-analysis has pointed out multiple concerns that may result in biased results. Among other problems, the analysis excluded vitamin D + calcium co-administration; the study did not account for dietary vitamin D and calcium intake; and calcium supplementation compliance was poor. No RCTs on bisphosphonates, raloxifene, teriparatide, hormone replacement therapy, denosumab, or vitamin D reported an increase in myocardial infarction.	
Risk of Cardiovascular (CV) Death **SOE: Not Reported** One RCT comparing zoledronic acid vs placebo found no significant differences. One RCT comparing risedronate vs placebo found no significant differences. One pooled OR for three studies showed no significant differences between raloxifene and placebo for risk of cardiovascular death. No RCTs of alendronate, ibandronate, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting CV death were found.	No studies were identified.
Risk of Breast Cancer **SOE: High** One RCT on alendronate found no significant difference. Two RCTs studying raloxifene vs placebo reported no significant increase in risk for breast cancer. One trial showed a significant decrease in the risk of breast cancer after the discontinuation of menopausal hormone therapy.	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
No RCTs of risedronate, ibandronate, zoledronic acid, teriparatide, denosumab, vitamin D, or calcium reporting risk of breast cancer were found.	
Risk of Colon and GI Cancer **SOE: Not Reported** One large case control study of bisphosphonate (alendronate, risedronate, ibandronate, and zoledronic acid) use and GI cancers in the UK found no significant differences in the risk for colorectal cancer between users of bisphosphonates and matched controls. No RCTs on raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting risk of colon cancer were found.	No studies were identified.
Risk of Esophageal Cancer **SOE: Insufficient** Four large observational studies on the incidence of esophageal cancer among bisphosphonate users were found. A cohort study found no difference in the risk for esophageal cancer between cohorts. A case-control study that used the same database as the cohort study found that individuals with at least one prescription for oral bisphosphonates had a significantly increased risk for esophageal cancer. When pooled, two additional large observational studies found a significantly increased risk for esophageal cancer in the bisphosphonate-treated group. A case-control study found that individuals diagnosed with esophageal cancer had an increased likelihood of bisphosphonate use. A case-control study found no increased risk for esophageal cancer for bisphosphonate users. No RCTs of raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting the risk of esophageal cancer were found.	No studies were identified.
Risk of Lung Cancer **SOE: Not Reported** One RCT on risedronate found no significant difference in the risk of lung cancer.	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
No trials of alendronate, ibandronate, zoledronic acid, teriparatide, hormone placement therapy, denosumab, vitamin D, or calcium reporting risk of lung cancer were found.	
Risk of GI Events (including nausea) **SOE: High** A pooled analysis showed alendronate had a slightly increased risk of mild upper GI events. Alendronate participants had higher odds of mild upper GI events in head-to-head trials vs. menopausal hormone therapy. Pooled analysis showed alendronate users to be at an increased risk for mild GI events in head-to-head trials vs denosumab. Two RCTs found no significant difference in the incidence of PUBs between raloxifene and placebo. One RCT found no significant difference in the incidence of mild GI events between raloxifene and placebo. One placebo-controlled trial showed an increase in reflux and esophageal complaints as well as other mild upper GI adverse events with use of denosumab. One trial assessing vitamin D reported no significant differences between treatment and placebo groups regarding GI adverse events. No trials of ibandronate, risedronate, zoledronic acid, teriparatide, or calcium reporting risk of lung cancer were found.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 5.4% of the 351 adverse events reports (approximately 19 reports) were nausea.[4]
Risk of Arthritis and Arthralgia **SOE: High** Pooled analysis of two RCTs comparing alendronate vs placebo showed a decreased risk for arthritis and arthralgia in the treated group. Analysis of four pooled trials comparing zoledronic acid vs placebo	A double-blind RCT (n=143) compared the use of raloxifene at 60 mg/day or 120 mg/day to a control group receiving supplements of calcium (750 mg/day) and vitamin D (400 IU/day) in postmenopausal osteoporotic women (mean age=68.4). Results show significant incidences of arthralgia (p=0.027).[5]

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
reported an increased risk of arthritis and arthralgia in the treated group. One RCT of ibandronate vs placebo found no significant difference. Five RCTs of risedronate vs placebo found no significant differences. In two head-to-head trials of alendronate vs denosumab, alendronate was significantly less likely to be associated with arthritis and arthralgia. One placebo-controlled study found no significant effect on reports of arthritis and arthralgia with use of raloxifene. No RCTs of teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting arthritis and arthralgia were found.	
Risk of Myalgia, Cramps, and Limb Pain **SOE: Moderate** Pooled analysis of two trials comparing ibandronate vs placebo showed an increase risk for myalgia, cramps, and limb pain in the treatment group. Pooled analysis of six trials comparing zoledronic acid vs placebo showed an increase risk of myalgia, cramps, and limb pain in the treatment group. A pooled analysis of ten trials found an increased risk with raloxifene for myalgia, cramps, and limb pain. No RCTs of alendronate, risedronate, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting myalgia, cramps, or limb pain were found.	No studies were identified.
Risk of Osteonecrosis **SOE: High** One trial, one post hoc analysis of three trials, two large observational studies, and a review of 2,408 cases of osteonecrosis of the jaw in	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
patients taking bisphosphonates for osteoporosis prevention or treatment found that the incidence of osteonecrosis of the jaw in this group was small, ranging from less than one to 28 cases per 100,000 person-years of treatment. No RCTs on raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reported an increase in osteonecrosis.	
Risk of Atypical Subtrochanteric Fractures of Femur **SOE: Low** Limited data from clinical trials and observational studies (a post-hoc analysis, a case series, and a task force report form the American Society of Bone and Mineral Research) support a possible association between bisphosphonate use and atypical subtrochanteric fractures of the femur. Data are not consistent; nevertheless these data were sufficient for FDA to issue a warning regarding this possible adverse event. No RCTs on raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reported an increase in atypical subtrochanteric fractures of the femur.	No studies were identified.
Adverse Fracture Healing **SOE: Not Reported** One post hoc analysis showed no association between the timing of infusion of zoledronic acid and delayed fracture healing. One nested case-control study showed an association between bisphosphonate uses among individuals with nonunion humeral fractures found an increase in odds of nonunion fractures among patients who took bisphosphonates in the post-fracture period regardless of prior history of osteoporosis or fracture. No RCTs on raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium vs placebo reported an increase in adverse fracture healing.	No studies were identified.
Risk of Hypercalcemia	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
SOE: Moderate Teriparatide-treated participants showed a significant increase in hypercalcemia, according to a pooled analysis of three placebo-controlled trials. No RCTs comparing the effects of bisphosphonates, raloxifene, hormone replacement therapy, denosumab, vitamin D, or calcium reporting a risk of hypercalcemia were found.	
Risk of Hypercalciuria **SOE: Not Reported** One placebo-controlled trial of vitamin D showed an increased risk for hypercalciuria in the treatment group. No RCTs comparing the effects of bisphosphonates, raloxifene, teriparatide, hormone replacement therapy, denosumab or calcium reporting a risk of hypercalciuria were found.	No studies were identified.
Risk of Hot Flashes **SOE: High** A pooled analysis of eight placebo-controlled trials found an increased risk with raloxifene of hot flashes. No RCTs of bisphosphonates, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting hot flashes were found.	No studies were identified.
Risk of Headaches and Dizziness **SOE: Moderate** A pooled analysis of two trials of teriparatide found an increased risk of headaches. No RCTs of bisphosphonates, raloxifene, hormone replacement therapy, denosumab, vitamin D, or calcium reporting headaches and/or dizziness were found.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 4.3% of the 351 adverse events reports (approximately 15 reports) were headaches.[4] A double-blind RCT (n=143) compared the use of raloxifene at 60 mg/day or 120 mg/day to a control group receiving supplements of calcium (750 mg/day) and vitamin D (400 IU/day) in postmenopausal osteoporotic women (mean age=68.4). Compared to control, raloxifene was associated with more dizziness in non-hypotensive patients (p=0.024).[5]

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
Risk of Rash **SOE: High** A pooled analysis of four trials of denosumab found an increased risk of rash but no increase in the risk for injection-site reactions. No RCTs of bisphosphonates, raloxifene, teriparatide, hormone replacement therapy, vitamin D, or calcium reporting rash were found.	No studies were identified.
Risk of Hypocalcemia **SOE: Moderate** A small number of clinical trials have reported an increased risk of hypocalcemia in patients treated with alendronate and zoledronic acid. No RCTs of ibandronate, risedronate, raloxifene, teriparatide, hormone replacement therapy denosumab, vitamin D, or calcium reporting hypocalcemia were found.	No studies were identified.
Risk of Infection **SOE: High** A pooled analysis of four trials of denosumab found an increased risk for infection in the treatment group. No RCTs of bisphosphonates, raloxifene, teriparatide, hormone replacement therapy, vitamin D, or calcium reporting infection were found.	No studies were identified.
Risk of Death **SOE: Not Reported** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of death were not included in the original review.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 4.1% of the 351 adverse events reports (approximately 14 reports) were death.[4]
Transient Ischemic Attack **SOE: Insufficient** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of transient ischemic were not included in the original review.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 4.1% of the 351 adverse events reports (approximately 14 reports) were transient ischemic attack.[4]

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
Risk of Arrhythmia **SOE: Insufficient** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of arrhythmia were not included in the original review.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 2.5% of the 351 adverse events reports (approximately 9 reports) were arrhythmias.[4]
Risk of Dyspnea **SOE: Insufficient** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of dyspnea were not included in the original review.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 2.5% of the 351 adverse events reports (approximately 9 reports) were dyspnea.[4]
Risk of Hypertension **SOE: Insufficient** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of hypertension were not included in the original review.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 2.5% of the 351 adverse events reports (approximately 9 reports) were hypertension.[4]
Risk of Hypotension **SOE: Insufficient** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of hypotension were not included in the original review.	A double-blind RCT (n=143) compared the use of raloxifene at 60 mg/day or 120 mg/day to a control group receiving supplements of calcium (750 mg/day) and vitamin D (400 IU/day) in postmenopausal osteoporotic women (mean age=68.4). There was a 6 mmHg decrease in systolic blood pressure in groups using raloxifene (p=0.028). None of the patients who reported dizziness were found to be hypotensive.[5]
Risk of Dermatological Conditions **SOE: Insufficient** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of dermatological conditions were not included in the original review.	In a three-year, randomized, placebo-controlled clinical trial in postmenopausal women with osteoporosis (n=7,808), patients who were treated with 60 mg of denosumab (vs placebo) every six months for three years had more incidences of eczema and cellulitis.[1]
Risk of Falling **SOE: Insufficient** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of dermatological conditions were not included in the original review.	In a three-year, randomized, placebo-controlled clinical trial in postmenopausal women with osteoporosis (n=7,808), patients who were treated with 60 mg of denosumab (vs placebo) every six months for three years had fewer incidences of falling and concussions.[1]

Abbreviations: CVA=Cerebrovascular Accident; FDA=Food and Drug Administration; GI=Gastrointestinal; SOE=Strength of Evidence

Table 5. Key Question 5a: How often should patients be monitored (via measurement of bone mineral density) during therapy?

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
BMD Monitoring **SOE: Insufficient** No RCTs that directly compared various schedules of serial BMD monitoring during osteoporosis pharmacotherapy in relation to optimal fracture prediction were found.	No studies were identified.
BMD Monitoring Predicting Anti-fracture Benefits During Pharmacotherapy **SOE: High** Studies from the Fracture Intervention Trial (FIT) of alendronate vs. placebo (5 mg daily for the first two years, then 10 mg/day) among postmenopausal women showed that among participants taking at least 60% of assigned study medication, women who gained 0% to% of BMD after 1-2 years during treatment had a decrease in vertebral risk of 51% after 3-4 years of follow-up. However, women who had lost 0% to 4% of lumbar spine BMD during alendronate therapy had a 60% lower risk of vertebral fractures compared to their counterparts assigned to placebo. The study concluded that monitoring bone mineral density in postmenopausal women in the first three years after starting treatment with a potent bisphosphonate is unnecessary and may be misleading. A study examining participants assigned 2.5 mg of risedronate vs 5 mg of risedronate per day, incidence of nonvertebral fractures during three years of follow up was not different between women whose spine BMD increased. A similar study found no significant difference in risk of nonvertebral fractures between women whose femoral neck BMD increased or decreased. Thus, greater increases in BMD did not necessarily predict greater decreases in vertebral fracture risk. A post hoc pooled analysis of two RCTs, increases in hip and lumbar spine BMD during oral or intravenous ibandronate administration were statistically significantly associated with vertebral fracture rate. However, changes in total hip and lumbar spine BMD explained only 23%-37% of the antifracture effect at 2 and 3-year follow up. Raloxifene The reduction of risk for fracture analyzed in the three year	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
MORE trial on raloxifene showed no difference in risk fracture regardless of the amount of change in lumbar spine BMD at three years. Irrespective of femoral neck and lumbar spine BMD, raloxifene decreased risk of new fractures by 38% in year one and 41% by year three. In the Fracture Prevention Trial (teriparatide 20 or 40 µg/day vs. placebo in postmenopausal women), women who lost greater than 4% at the femoral neck during the first 12 months of teriparatide treatment had significant reductions in vertebral fracture risk compared to placebo during a median of 19 month follow-up. Compared to women assigned to placebo, the decrease in vertebral fracture risk in women assigned to teriparatide was similar across categories of femoral neck BMD change from baseline to 12 months. Vertebral fracture risk was decreased among women who lost femoral neck BMD during teriparatide therapy. Among women assigned to teriparatide, increases in spine BMD accounted for 30% to 41% of the reduction in vertebral fracture risk. Greater increases in BMD did not necessarily predict greater decreases in fracture risk. No studies reporting effect of BMD monitoring on antifracture benefits during pharmacotherapy for ibandronate, zoledronic acid, denosumab, menopausal hormone therapy, vitamin D, or calcium were found.	
Ability to Predict Anti-fracture Events in Various Pharmacotherapies **SOE: Insufficient** No RCTs that directly compared the ability of monitoring to predict anti-fracture effects among various pharmacotherapies were found.	No studies were identified.

Abbreviations: BMD=Bone Mineral Density; SOE=Strength of Evidence

Table 6. Key Question 5b: How does the antifracture benefit vary with long-term continued use of pharmacotherapy?

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
Long-Term Use of Pharmacotherapies on Fracture Risk **SOE: Moderate**	No studies were identified.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)
One large RCT showed that after 5 years of initial alendronate therapy, vertebral fracture risk and nonvertebral fracture risk were lower if alendronate was continued for an additional 5 years instead of discontinued. No studies reporting effect of long-term use of ibandronate, risedronate, zoledronic acid, raloxifene, teriparatide, menopausal hormone therapy, denosumab, vitamin D, or calcium on fracture risk were found.	
Long-Term Use of Pharmacotherapies and BMD on Fracture Risk **SOE: Low** A post hoc analysis of a large RCT showed that after 5 years of initial alendronate therapy, there were statistically significant nonvertebral fracture risk reductions for women who at baseline had no vertebral fracture but had a BMD score of –2.5 or less. No studies reporting effect of long-term use of ibandronate, risedronate, zoledronic acid, raloxifene, teriparatide, menopausal hormone therapy, denosumab, vitamin D, or calcium and BMD on fracture risk were found.	No studies were identified.

Abbreviations: BMD=Bone Mineral Density; RCT=Randomized Controlled Trial; SOE=Strength of Evidence

Abstracts from Relevant Literature/References:

1. Lewiecki EM. Clinical use of denosumab for the treatment for postmenopausal osteoporosis. Current medical research and opinion. Dec 2010;26(12):2807-2812.

   Denosumab is a fully human monoclonal antibody with high affinity and specificity for human receptor activator of nuclear factor kappa B ligand (RANKL), the principal regulator of osteoclastic bone resorption. By binding to RANKL, denosumab prevents it from binding to its receptor on the cell surface of pre-osteoclasts and mature osteoclasts, thereby reducing the formation, activity, and survival of osteoclasts and inhibiting osteoclastic bone resorption. In a large, randomized, placebo-controlled clinical trial in postmenopausal women with osteoporosis, denosumab 60 mg administered subcutaneously every 6 months reduced levels of bone turnover markers, increased bone mineral density, and reduced the risk of vertebral fractures, hip fractures, and non-vertebral fractures. There was no significant difference between denosumab and placebo in the overall risk of adverse events or serious adverse events. Denosumab was associated with a significant increase in the risk of eczema and cellulitis, and a significant decrease in the risk of falling and concussions. Denosumab recently received

regulatory approval for the treatment of postmenopausal women with osteoporosis at high risk for fracture, with no dose adjustment in patients with renal impairment. Denosumab is a new therapeutic option to reduce fracture risk in women with postmenopausal osteoporosis, especially for those with impaired renal function or with intolerance or poor response to oral therapy.

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2. Sinaki M, Mikkelsen BA. Postmenopausal spinal osteoporosis: flexion versus extension exercises. *Archives of physical medicine and rehabilitation.* Oct 1984;65(10):593-596.

   Fifty-nine women with postmenopausal spinal osteoporosis and back pain were instructed in a treatment program that included extension exercises (E) for 25 patients, flexion exercises (F) for 9, combined (E + F) exercises for 19, or no therapeutic exercises (N) for 6. Ages ranged from 49 to 60 years (mean, 56 years). Follow-up ranged from one to six years (means for the groups, 1.4 to 2 years). All patients had spine x-ray studies before treatment and at follow-up, at which time any further wedging and compression fractures were recorded. Additional fractures occurred as follows: group E, 16%; F, 89%; E + F, 53%; and N, 67%. In comparison with group E, the occurrence of wedging or compression fractures was significantly higher in group F (p less than 0.001) and group E + F (p less than 0.01). This study suggests that a significantly higher number of vertebral compression fractures occur in patients with postmenopausal osteoporosis who followed a flexion exercise program compared with those using extension exercises. Extension or isometric exercises seem to be more appropriate for patients with postmenopausal osteoporosis.

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3. Vestergaard P, Hermann P, Jensen JE, Eiken P, Mosekilde L. Effects of paracetamol, non-steroidal anti-inflammatory drugs, acetylsalicylic acid, and opioids on bone mineral density and risk of fracture: results of the Danish Osteoporosis Prevention Study (DOPS). Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. Apr 2012;23(4):1255-1265.

   Pain medication has been associated with fractures. We found higher weight in paracetamol and non-steroidal anti-inflammatory drugs (NSAID) users and lower vitamin D levels in opioid and acetylsalicylic acid users. None of the pain medications influenced bone mineral density or loss. NSAID were associated with an increased fracture risk. INTRODUCTION: To study the effects of use of paracetamol, non-steroidal anti-inflammatory drugs (NSAID), acetylsalicylic acid (ASA), and opioids on bone mineral density (BMD) and risk of fractures. METHODS: Two-thousand sixteen perimenopausal women followed for 10 years as part of a partly randomised comprehensive cohort study on hormone therapy (HT). BMD was measured at baseline and after 10 years by DXA (Hologic). RESULTS: Paracetamol users were heavier (70.4 +/- 13.4 vs. 67.7 +/- 11.9 kg, 2p < 0.01) than non-users. NSAID users were heavier (71.6 +/- 15.6 vs. 67.8 +/- 11.9 kg, 2p = 0.04) than non-users. ASA users had lower 25-hydroxy-vitamin D (25OHD) levels (21.9 +/- 9.3 vs. 25.3 +/- 12.4 ng/ml, 2p < 0.01) than non-users. Opioid users had lower 25OHD (21.4 +/- 8.4 vs. 25.2 +/- 12.3 ng/ml) and lower intake of

vitamin D (2.2 +/- 1.1 vs. 3.1 +/- 3.0 mug/day, 2p < 0.01) than non-users. Despite these differences, no baseline differences were present in spine, hip, forearm or whole body BMD. Over 10 years, no differences were present in BMD alterations except a small trend towards a higher BMD gain in the spine in users of paracetamol, NSAID, ASA, and opioids compared to non-exposed. After adjustment, NSAID exposed sustained more fractures (HR = 1.44, 95% CI 1.07-1.93) than non-users. For users of paracetamol and opioids, a non-significant trend towards more fractures was present after adjustment. For ASA users, no excess risk of fractures was present. CONCLUSION: Significant differences exist between subjects exposed to pain medications and non-users. Despite an absence of an effect over time on BMD, users of NSAID experienced more fractures than expected. The reasons for this have to be explored in further studies.

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4. Fahrleitner-Pammer A, Langdahl BL, Marin F, et al. Fracture rate and back pain during and after discontinuation of teriparatide: 36-month data from the European Forsteo Observational Study (EFOS). Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. Oct 2011;22(10):2709-2719.

   In this observational study in postmenopausal women with severe osteoporosis, the incidence of fractures was decreased during 18 months of teriparatide treatment with no evidence of further change in the subsequent 18-month post-teriparatide period when most patients took other osteoporosis medications. Fracture reduction was accompanied by reductions in back pain. INTRODUCTION: To describe fracture outcomes and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment and 18 months post-teriparatide in normal clinical practice. METHODS: The European Forsteo Observational Study (EFOS) was a prospective, multinational, observational study. Data on incident clinical fractures and back pain (100 mm Visual Analogue Scale [VAS] and questionnaire) were collected. Fracture data were summarised in 6-month intervals and analysed using logistic regression with repeated measures. Changes from baseline in back pain VAS were analysed using a repeated measures model. RESULTS: A total of 208 (13.2%) of 1,576 patients sustained 258 fractures during 36 months of follow-up: 34% were clinical vertebral fractures and 66% non-vertebral fractures. The adjusted odds of fracture were reduced during teriparatide treatment and there was no evidence of further change in the 18-month post-teriparatide period, during which 63.3% patients took bisphosphonates. A 74% decrease in the adjusted odds of fracture in the 30- to <36-month period compared with the first 6-month period was observed (p < 0.001). Back pain decreased during teriparatide treatment and this decrease was sustained after teriparatide discontinuation. Adjusted mean back pain VAS decreased by 26.3 mm after 36 months (p < 0.001) from baseline mean of 57.8 mm. CONCLUSIONS: In a real-life clinical setting, the risk of fracture decreased during teriparatide treatment, with no evidence of further change after teriparatide was discontinued. The changes in back pain seen during treatment were maintained for at least 18 months after teriparatide discontinuation. These results should be interpreted in the context of the design of an observational study.

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5. Lufkin EG, Whitaker MD, Nickelsen T, et al. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. Nov 1998;13(11):1747-1754.

Raloxifene is a selective estrogen receptor modulator that in experimental animals acts as an estrogen receptor antagonist in breast and endometrium but as an estrogen receptor agonist in the skeletal and cardiovascular systems. We conducted a 1-year prospective, randomized, double-blind trial in 143 postmenopausal osteoporotic women (mean +/- SD age, 68.4+/-5.0 years) with at least one prevalent vertebral fractures and low bone mineral density (BMD), comparing groups receiving raloxifene at 60 mg/day (RLX60) or 120 mg/day (RLX120) and a control group receiving supplements of 750 mg/day of calcium and 400 IU/day of vitamin D. There were no differences among groups in the occurrence of uterine bleeding, thrombophlebitis, breast abnormalities, or increased endometrial thickness (assessed by ultrasonography). As compared with controls, the changes in values over 1 year for RLX60 and RLX120, respectively, were significant for serum bone alkaline phosphatase (-14.9%, -8.87%), serum osteocalcin (-20.7%, -17.0%), and urinary C-telopeptide fragment of type I collagen/creatinine (-24.9%, -30.8%), markers of bone turnover; for serum total cholesterol (-7.0% for RLX60) and low density lipoprotein cholesterol (LDL) (-11.4% for RLX60) and for the LDL/HDL cholesterol ratio (-13.2%, -8.3%). BMD increased significantly in the total hip (1.66% for RLX60) and ultradistal radius (2.92%, 2.50%). There were nonsignificant trends toward increases over controls in BMD for lumbar spine, total body, and total hip (for RLX120). Using a >15% cutoff definition, raloxifene had no effect on incident fractures, but using a >30% cutoff, there was a dose-related reduction ($p = 0.047$). We conclude that raloxifene therapy is well tolerated, reduces serum lipids, and does not stimulate the uterus or breasts. It has beneficial effects on bone, although, under the conditions of this study, these appear to be of a smaller magnitude than have been reported with estrogen therapy.

Appendix G. Summary Table

No relevant FDA boxed warnings were identified.

Table 1. Key Question 1: What are the comparative benefits in fracture risk reduction among the following treatments for low bone density?

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
Bisphosphonates: Vertebral Fractures **SOE: High** In two pooled analyses (two RCTs) of alendronate vs placebo, the treatment group has been shown to reduce the risk of vertebral fractures among postmenopausal women with osteoporosis. In two pooled analyses (three RCTs) of risedronate vs placebo, the treatment group has been shown to reduce the risk of vertebral fractures among postmenopausal women with osteoporosis at a dose of 5.0 mg (decreased risk of 58% [1 RCT]), and does not significantly reduce the risk of vertebral fractures at 35 mg per week (3 RCTs). No studies evaluating 2.5 mg per day or 30 mg per week were found. In one pooled analysis (one RCT) of ibandronate vs placebo, the treatment group has been shown to reduce the risk of vertebral fractures among postmenopausal women with osteoporosis.	No studies were identified.	One expert believed the conclusions to still be current, but suggested that using trials with bone mineral density as an endpoint may provide useful information. The second reviewer believed conclusions to still be current.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
In two RCTs of zoledronic acid vs placebo, the treatment group has been shown to reduce the risk of vertebral fractures among postmenopausal women with osteoporosis at a dose of 5.0 mg (one time only [one RCT]) and 2.0 mg (every six months [one RCT]). No studies evaluating 4.0 mg (one time only), 1 mg (every three months), 0.5 mg (every three months), or 0.25 mg (every three months) were found.			
Bisphosphonates: Non-Vertebral Fractures **SOE: High** In one pooled analysis (two RCTs) of alendronate vs placebo, the treatment group has been shown to reduce the risk of non-vertebral fractures among postmenopausal women with osteoporosis. In two pooled analyses (four RCTs) of risedronate vs placebo, the treatment group has been shown to reduce the risk of nonvertebral fractures among postmenopausal women with osteoporosis at a dose of 2.5 mg per day (decreased risk of 71% [1 RCT]) and 35 mg per week (two RCTs). While a dose of 5.0 mg per day in men at 12 months does not significantly reduce fractures (two RCTs), a dose of 5.0 mg per day at 24 month does significantly reduce the risk of nonvertebral fractures in men. No studies evaluating	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
30 mg per week were found. In two pooled analysis (no new RCTs) of ibandronate vs placebo, the treatment group has been shown to reduce the risk of non-vertebral fractures among postmenopausal women with osteoporosis. In two RCTs of zoledronic acid vs placebo, the treatment group has been shown to reduce the risk of nonvertebral fractures among postmenopausal women with osteoporosis at a dose of 5.0 mg (one time only [one RCT]) and 2.0 mg (every six months [one RCT]). No studies evaluating 4.0 mg (one time only), 1 mg (every three months), 0.5 mg (every three months), or 0.25 mg (every three months) were found.			
Bisphosphonates: Hip Fractures **SOE: High** In one pooled analysis (no new RCTs) of alendronate vs placebo, the treatment group has been shown to reduce the risk of hip fractures among postmenopausal women with osteoporosis by 70%. In one pooled analysis (three RCTs) of risedronate vs placebo, the treatment group has been shown to reduce the risk of hip fractures among postmenopausal women with osteoporosis at a dose of 2.5 mg per	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
day (decreased risk of 71% [three RCT]). No studies evaluating 5.0 mg per day, 30 mg per week, or 35 mg per week were found. No studies of hip risk fracture in ibandronate vs placebo were found. In one RCT of zoledronic acid vs placebo, the treatment group has been shown to reduce the risk of hip fractures among postmenopausal women with osteoporosis at a dose of 5.0 mg (one time only [one RCT]). No studies evaluating 4.0 mg (one time only), 2.0 mg (every six months), 1 mg (every three months), 0.5 mg (every three months), or 0.25 mg (every three months) were found.			
Bisphosphonates: Wrist Fractures **SOE: Low** In one pooled analysis (no new RCTs) of alendronate vs placebo, the treatment group has been shown to not reduce the risk of wrist fractures among postmenopausal women with osteoporosis. In one pooled analysis (one RCT) of risedronate vs placebo, the treatment group has been shown to not reduce the risk of wrist fractures among postmenopausal women with osteoporosis at a dose of 5.0 mg per day. No studies evaluating 2.5 mg per day, 30 mg per week, or 35 mg per	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
week were found. No studies of wrist risk fracture in ibandronate vs placebo were found. No studies of wrist risk fracture in zoledronic acid vs placebo were found.			
SERMs (raloxifene): Vertebral Fractures **SOE: High** Raloxifene reduces the risk of vertebral fractures (two RCTs) among postmenopausal women with osteoporosis.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
SERMs (raloxifene): Non-Vertebral Fractures **SOE: High** Raloxifene does not reduce the risk of nonvertebral fractures (two RCTs) among postmenopausal women with osteoporosis.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
SERMs (raloxifene): Hip Fractures **SOE: High** Raloxifene does not reduce the risk hip fractures (one RCT) among postmenopausal women with osteoporosis.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
SERMs (raloxifene): Wrist Fractures **SOE: High** Raloxifene does not reduce the risk of wrist fractures (one RCT) among postmenopausal women with osteoporosis.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
PTH (teriparatide): Vertebral Fractures **SOE: High** In the RCT with the fewest number of vertebral fracture events, vertebral fracture risk was no different with teriparatide than placebo; however, the remainder of the RCTs demonstrated vertebral fracture risk to be statistically significantly lower with teriparatide than with placebo.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
PTH (teriparatide): Non-Vertebral Fractures **SOE: High** In one pooled analysis (5 RCTs) of teriparatide vs placebo, the treatment group has been shown to reduce the risk of non-vertebral fractures among postmenopausal women with osteoporosis.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
PTH (teriparatide): Hip Fractures No studies of hip risk fracture in teriparatide vs placebo were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
PTH (teriparatide): Wrist Fractures No studies of wrist risk fracture in teriparatide vs placebo were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Menopausal Hormone Therapy: Vertebral Fractures **SOE: High** Menopausal hormone therapy does not statistically significantly reduce the risk of vertebral fractures in postmenopausal women (one trial).	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Menopausal Hormone Therapy: Non-Vertebral Fractures **SOE: High** Menopausal hormone therapy does not statistically significantly reduce the risk of nonvertebral fractures in postmenopausal women (one trial).	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Menopausal Hormone Therapy: Hip Fractures No studies of risk of hip fracture in menopausal hormone therapy vs placebo were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Menopausal Hormone Therapy: Wrist Fractures No studies of risk of wrist fracture in menopausal hormone therapy vs placebo were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Denosumab: Vertebral Fractures	In a three-year, randomized,	See above.	The conclusion in this portion of

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
SOE: High In two RCTs of denosumab vs placebo, the treatment group has been shown to reduce the risk of vertebral fractures among postmenopausal women with osteoporosis.	placebo-controlled clinical trial in postmenopausal women with osteoporosis (n=7,808), patients who were treated with 60 mg of denosumab (vs placebo) every six months for three years had fewer vertebral fractures.[1]		the original systematic review is likely current.
Denosumab: Non-Vertebral Fractures **SOE: High** In two RCTs of denosumab vs placebo, the treatment group has been shown to reduce the risk of non-vertebral fractures among postmenopausal women with osteoporosis.	In a three-year, randomized, placebo-controlled clinical trial in postmenopausal women with osteoporosis (n=7,808), patients who were treated with 60 mg of denosumab (vs placebo) every six months for three years had fewer non-vertebral fractures.[1]	See above.	The conclusion in this portion of the original systematic review is likely current.
Denosumab: Hip Fractures **SOE: High** In one RCT of denosumab vs placebo, the treatment group has been shown to reduce the risk of hip fractures among postmenopausal women with osteoporosis.	In a three-year, randomized, placebo-controlled clinical trial in postmenopausal women with osteoporosis (n=7,808), patients who were treated with 60 mg of denosumab (vs placebo) every six months for three years had fewer hip fractures.[1]	See above.	The conclusion in this portion of the original systematic review is likely current.
Denosumab: Wrist Fractures No studies of wrist risk fracture in denosumab vs placebo were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Denosumab: Other Fractures In one meta-analysis (three RCTs) of denosumab vs placebo, the treatment group has been shown to reduce the risk of all fracture types among postmenopausal women with osteoporosis.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
In one pooled analysis of denosumab vs placebo, the treatment group has been shown to reduce the risk of clinical fractures among postmenopausal women with osteoporosis.			
Calcium: Vertebral Fractures **SOE: Moderate** Two RCTs showed the risk of vertebral fractures to be not statistically different with calcium compared to placebo.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Calcium: Non-Vertebral Fractures **SOE: Moderate** Two RCTs showed the risk of non-vertebral fractures to be not statistically different with calcium compared to placebo.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Calcium: Hip Fractures **SOE: Moderate** One pooled estimate showed a 64% increase in risk of hip fracture associated with calcium supplementation. However, another pooled estimate of a meta-analysis with almost ten times more participants found a 25% reduction in risk of hip fracture with calcium compared to a placebo. Therefore, data on the effects of calcium supplementation on hip fractures is conflicting.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Calcium: Wrist Fractures **SOE: Moderate** Two RCTs showed the risk of wrist	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
fractures to be not statistically different with calcium compared to placebo.			
Calcium: All Fractures **SOE: Moderate** In one systematic review of 16 RCTs of calcium vs placebo, the treatment group has been shown to reduce the risk of all fractures among postmenopausal women with osteoporosis. One new RCT was identified.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Vitamin D: Vertebral Fractures **SOE: Low-Moderate** In a pooled analysis of vitamin D vs placebo, the treatment group has been shown to reduce the risk of vertebral fractures among postmenopausal women with primary osteoporosis, but was not associated with a reduction in vertebral fracture risk in those with prior fractures, women with severe osteoporosis, or those taking glucocorticoid treatment. Of note, results are inconsistent across pooled analyses. Four new RCTs were identified.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Vitamin D: Nonvertebral Fractures **SOE: Low-Moderate** In a meta-analysis of vitamin D vs placebo, the treatment group has been shown to reduce the risk of nonvertebral fractures among elderly women not selected for prior osteoporotic fracture, vitamin D	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
analogues (alfacalcidol and calcitriol) for primary osteoporosis, and standard vitamin D for primary osteoporosis. In contrast, two systematic reviews report that the following were not associated with statistically significant reductions in nonvertebral fracture risk: alfacalcidol, calcitriol, or vitamin D among people not selected on the basis of prior osteoporotic fracture, calcitriol among women with severe osteoporosis. Six new RCTs were identified.			
Vitamin D: Hip Fractures **SOE: Low-Moderate** For hip fracture, compared to placebo, alfacalcidol (vitamin D analogue) reduced relative risk of fracture by 84% (on systematic review). Both standard vitamin D and calcitriol (vitamin D analogue) were not statistically significantly more effective than placebo in reducing hip fracture risk among those who were not selected, nor among those who were selected, on the basis of previous osteoporotic fractures. One pooled estimate showed a statistically significantly increased risk of hip fracture in associated with injection of vitamin D compared to placebo. Seven new RCTs were identified.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
Vitamin D: Wrist Fractures **SOE: Insufficient** No studies of risk of wrist fracture in vitamin D vs placebo were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Vitamin D: All Fractures **SOE: Low-Moderate** The effect of vitamin D on fracture risk is uncertain. Among a number of meta-analyses, some reported a reduced risk for vitamin D relative to placebo, some did not. There was no reduction in fracture risk for vitamin D relative to placebo in a large, high quality RCT published after the meta-analyses.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Vitamin D + Calcium: Vertebral Fractures **SOE: Low-Moderate** When compared to placebo, vitamin D + calcium was not associated with statistically significant reductions in vertebral fractures.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Vitamin D + Calcium: Nonvertebral Fractures **SOE: Low-Moderate** In combination with calcium, vitamin D was associated with a statistically significant reduction in nonvertebral fracture risk among populations not selected on the basis of prior osteoporotic fractures in two systematic reviews. Standard vitamin D	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
doses of ≥700 IU/d + calcium are associated with statistically significant reductions in nonvertebral fracture risk among institutionalized persons. A third systematic review shows, among institutionalized persons, vitamin D + calcium was associated with a 15% decrease (statistically significant) in nonvertebral fracture risk. The same review reported that vitamin D + calcium was not associated with a statistically significantly decreased risk of nonvertebral fractures among those who were not selected on the basis of prior osteoporotic fractures, those who were selected on the basis of prior osteoporotic fractures, or among community-dwellers.			
Vitamin D + Calcium: Hip Fractures **SOE: Low-Moderate** Vitamin D + calcium (vs. placebo) was associated with statistically significantly reduced risk of hip fracture, ranging about 20% to 30%, in those selected or not selected on the basis of prior osteoporotic fractures (in some studies), not selected on the basis of low BMD, and among the institutionalized. Vitamin D + calcium did not decrease hip fracture risk more than placebo among community dwellers and general populations, even at high (≥700 IU/d) doses. Vitamin D doses of	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
10 µg were not effective in decreasing hip fracture risk unless they were given with calcium. Dosing of ≥700 IU of vitamin D was associated with a 28 percent lower risk of hip fractures among institutionalized persons. A new systematic review found that vitamin D supplementation did not statistically significantly alter hip fracture risk, but the authors analyzed vitamin D plus calcium and vitamin D jointly, in comparison to a reference group of placebo or calcium, respectively.			
Vitamin D + Calcium: Wrist Fractures **SOE: Insufficient** No studies of risk of wrist fracture in vitamin D + calcium vs placebo were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Exercise vs above agents **SOE: Insufficient** There are no data from RCTs to inform this question. One RCT that assessed the effect of a brief exercise program on fracture risk found a small decrease in risk of fractures among exercisers but the study was not powered to detect differences in fracture risk.	A RCT of 59 postmenopausal women with spinal osteoporosis and back pain (ages ranging from 49-60; mean=56) suggests that a significantly higher number of vertebral compression fractures occur in patients with postmenopausal osteoporosis who followed a flexion exercise program compared with those using extension exercises. Extension or isometric exercises seem to be more appropriate for patients with postmenopausal osteoporosis.[2]	See above.	This portion of the systematic review may not be current due to one study identified by our literature search which found an increased risk of vertebral compression fractures in patients following a flexion exercise program, while the evidence from the original systematic review was insufficient.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
Head-to-Head Comparisons **SOE: Insufficient** No new studies were identified for the following head-to-head comparisons: • Menopausal estrogen therapy vs bisphosphonate therapy • Bisphosphonate therapy vs calcium • Bisphosphonate therapy vs raloxifene • Alendronate vs risedronate in women with osteoporosis • Alendronate vs raloxifene among postmenopausal • Risedronate vs zoledronic acid • Etidronate vs calcitonin • Raloxifene vs menopausal estrogen therapy • Calcium vs Vitamin (or Vitamin D vs Calcium)	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Head-to-Head Comparisons • **Alendronate 10 mg/day vs teriparatide 20 µg/day** SOE: High In one 36-month RCT of people taking glucocorticoids, the odds of vertebral fracture and the risk of nonvertebral fracture were similar with alendronate 10 mg/day vs teriparatide 20 µg/day. • **Alendronate + Vitamin D vs Alendronate + Alfacalcidol** SOE: High In one 24-month RCT, the	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
odds of vertebral fracture were higher and the risk of nonvertebral fracture was similar with alendronate + vitamin D vs alendronate + alfacalcidol. • **Alfacalcidol + Prednisone + Alendronate vs Alfacalcidol + Prednisone** SOE: Low One RCT reported 90% lower odds of vertebral fracture with alfacalcidol + prednisone + alendronate vs alfacalcidol + prednisone. • **Alendronate vs. Alendronate + Calcium** SOE: Moderately High A RCT found three-fold higher odds of any of any clinical fracture with alendronate vs alendronate + calcium. • **Rocaltrol + Caltrate D vs Caltrate D** SOE: Moderately High A 12-month RCT found that rocaltrol + Caltrate D did not statistically significantly decrease the odds of vertebral fracture compared to Caltrate D. • **Menopausal Estrogen Therapy vs Vitamin D** SOE: Low One RCT examined vertebral and nonvertebral fractures in aggregate found that the odds			

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
of fracture were not statistically significantly different with menopausal estrogen +progestogen therapy vs vitamin D.			
Paracetamol, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Acetylsalicylic Acid (ASA), and Opioids: All Fractures **SOE: Not Reported** RCTs that directly compared paracetamol, NSAIDs, ASA, and opioids on fractures were not included in the original review.	A partially randomized comprehensive cohort study lasting 10 years (n=2016) examined premenopausal women compared the effect of NSAIDs, paracetamol, opioids, or acetylsalicylic acid on fracture incidence. After adjusting for relevant confounding variables, individuals receiving NSAIDs sustained more fractures than comparators and paracetamol and opioids were associated with a non-significant trend towards more fractures. No excess risk of fractures was associated with ASA.[3]	See above.	This portion of the systematic review may not be current due to one study identified by our literature search which found a significant increase risk of fractures in patients receiving NSAIDs and a non-significant increase in fractures in patients receiving paracetamol and opioids, while evidence from the original systematic review was not reported.

Abbreviations: RCT=Randomized Controlled Trial; SOE=Strength of Evidence

Table 2. Key Question 2: How does fracture risk reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density (borderline/low/severe), risk assessment score, prior fractures (prevention vs. treatment), age, sex, race/ethnicity, and glucocorticoid use?

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
Fracture Risk Reduction: Bone Mineral Density **SOE: Moderate** A post hoc analysis of FIT/FLEX in postmenopausal women with low	No studies were identified.	Both experts believed the conclusions of the original review to still be current.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
femoral neck BMD who had initially completed five years of alendronate therapy were assigned to receive another five years of therapy or five years of placebo. Both treatment arms received calcium and vitamin D. Incidence of nonvertebral and clinical fractures did not significantly differ among women who had lower baseline BMD vs women who had higher baseline BMD. A post hoc analysis of risedronate efficacy was performed among women with femoral T-score between -1 and -2.5 without prevalent fracture (osteopenia). Cumulative 2-year fragility fracture incidence was statistically significantly lower among women assigned to risedronate compared to placebo, and comparable to reductions seen in women with osteoporosis. No trials that included stratified analyses of fracture risk reduction based on bone mineral density while being treated with ibandronate, zoledronic acid, teriparatide, raloxifene, hormone replacement therapy, denosumab, vitamin D, or calcium were found.			
Fracture Risk Reduction: FRAX or Other Assessment Scores **SOE: Moderate** A post hoc analysis of the MORE	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
raloxifene trial failed to show significant differences in the risk of overall fracture and of incident morphometric vertebral fractures associated with raloxifene vs placebo according to the FRAX score. The post hoc analysis of raloxifene vs placebo did, however, show a 31% decrease in fractures in those 75 years or older, irrespective of FRAX score. At younger ages, effectiveness of raloxifene increased (decreased fracture risk). Additionally, raloxifene prevents fractures in postmenopausal women at low risk for fracture, as assessed by FRAX. No trials that included stratified analyses of fracture risk reduction using FRAX and other assessment scores while being treated with bisphosphonates, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium were found.			
Fracture Risk Reduction: Prior Fractures (Prevention vs Treatment) SOE: Moderate-Low A post hoc analysis of FIT/FLEX in postmenopausal women with low femoral neck BMD who had initially completed five years of alendronate therapy were assigned to receive another five years of therapy or five years of placebo. Both treatment arms received calcium and vitamin D. Cumulative incidence of nonvertebral	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
and clinical vertebral fractures did not significantly differ among women who had prevalent vertebral fractures at baseline. In a post hoc analysis of the FIT trial with the same 5-year extension as the previously described study, among women with prevalent vertebral fracture at baseline, continued alendronate reduced the risk of clinical (but not morphometric) vertebral fractures, but not morphometric or nonvertebral fractures. In contrast, among women without vertebral fractures at baseline, alendronate continuation reduced nonvertebral fractures among women with baseline femoral neck T-score ≤-2.5, but not with T-score between -2 and -2.5. An extension of the MORE trial of raloxifene examined the relative efficacy of raloxifene among women with, compared to without, prevalent vertebral fractures. Although raloxifene did not statistically significantly influence nonvertebral fracture risk, raloxifene did decrease the risk of major nonvertebral fracture (clavicle, humerus, wrist, pelvis, hip, lower leg) among women with prevalent vertebral fracture, but not among women without prevalent vertebral fracture at baseline. A post hoc analysis examined the effects of raloxifene on new vertebral			

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
fractures according to the presence or absence of prevalent fractures. The efficacy of raloxifene compared to placebo on decreasing vertebral fractures did not differ statistically significantly between women with and without prevalent fractures, (-8.21%, -0.75% vs. -2.83%, -1.21%, respectively). Among postmenopausal women with osteoporosis who were randomized to teriparatide therapy in the Fracture Prevention Trial, the absolute benefit of teriparatide was greater among women with the highest number and severity of prevalent vertebral fractures. No trials that included stratified analyses of fracture risk reduction by prior fractures while being treated with ibandronate, risedronate, zoledronic acid, hormone replacement therapy, denosumab, vitamin D, or calcium were found.			
Fracture Risk Reduction: Age **SOE: High** A post hoc analysis examined the relationship between age and the effect of risedronate treatment on fracture risk among postmenopausal women with osteoporosis. Irrespective of age, when compared to placebo, risedronate decreased the risk for any fracture, clinical fracture, nonvertebral fracture, and morphometric vertebral	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
fracture statistically significantly. In a post hoc analysis of postmenopausal women with osteoporosis, zoledronic acid significantly reduced clinical fractures, clinical vertebral fractures, and non-vertebral fractures across age groups (younger than 75 years old and equal to or older than 75 years old). However, only women younger than 75 had statistically significant reduction in hip fracture risk at three years. In a post hoc analysis of the HORIZON trial, zoledronic acid was reported to reduce vertebral fracture risk statistically significantly among women < 70 years old. However, no such treatment-age interaction was apparent for nonvertebral or hip fractures. In a post hoc analysis of the MORE raloxifene trial, antifracture effects of raloxifene vs. placebo were higher at younger ages. In a post hoc analysis of the Fracture Prevention Trial of postmenopausal women with osteoporosis, the relative risk of new vertebral fracture associated with teriparatide vs. placebo was similar among age subgroups. Risk of vertebral fracture among both women under 75 years and women 75 and over was statistically significant. For nonvertebral fractures the risk of			

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
fracture among women under 75 years was statistically significant, but not for women 75 years and over. However, treatment by age interactions was not statistically significant. Compared to placebo, annual intramuscular injection of vitamin D2 (ergocalciferol) 300,000 IU for 3 years among men and women aged 75 years and over did not reduce the risk of any first fracture, or wrist fracture, and it increased the risk of hip fracture. Associations of vitamin D2 with fracture risk did not vary according to sex, age, previous fracture, or mobility. No trials that included stratified analyses of fracture risk reduction by age while being treated with alendronate, ibandronate, hormone replacement therapy, denosumab, or calcium were found.			
Fracture Risk Reduction: Sex **SOE: Insufficient** Two trials of vitamin D reported fracture outcomes and included a sufficient number of men. A factorial cluster-randomized intervention study administered calcium carbonate and vitamin D3 (400 IU) tic immunity dwelling residents aged 66+. While fracture risk was statistically significantly reduced in women, fracture risk was not statistically significantly reduced in male	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
participants, possibly because fractures were relatively rare in elderly men. In the second trial, 9,440 men and women over the age of 75 living in Wales were randomized to receive 300,000 IU of ergocalciferol by IM injection. There was no statistically significant reduction in overall or site-specific fracture. Of note, women had an increased risk of wrist fracture in the vitamin D treatment group, while no significant differences were seen in men. While there are no published trials assessing the antifracture effects of any of the aforementioned agents (bisphosphonates, raloxifene, teriparatide, hormone replacement therapy, denosumab, or calcium) in men that are comparable to the large, international, placebo controlled trials that exist for women, nine trials that enrolled either all male subjects or had greater than 50% male subjects enrolled were found. However, these trials were either about special populations, were not powered to detect fracture risk outcomes, or were open-label.			
Fracture Risk Reduction: Race/Ethnicity **SOE: High** A post hoc analysis of the HORIZON trial in 323 Chinese women from Taiwan and Hong Kong found that	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
once-yearly zoledronic acid was associated with a significant 52% reduction in morphometric vertebral fracture at three years. A pooled analysis of two studies of Asian postmenopausal women with osteoporosis (one Chinese and one Japanese) examined the effects of raloxifene (60 mg/d or 120 mg/d vs. placebo). Raloxifene statistically significantly reduced the incidence of vertebral fractures and any new clinical fractures, but not nonvertebral fractures, compared to placebo. No trials that included stratified analyses of fracture risk reduction by age while being treated with alendronate, ibandronate, risedronate, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium were found.			
Fracture Risk Reduction: Glucocorticoid Use **SOE: Moderate-High** As reported in a 36-month RCT of people taking glucocorticoids, the odds of vertebral fracture were higher, and the risk of nonvertebral fracture was similar, with alendronate 10 mg/day vs. teriparatide 20 µg/day. A RCT newly identified for this report that examined vertebral and nonvertebral fractures in aggregate found that the odds of fracture were not	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
significantly different with menopausal estrogen + progestogen therapy vs. vitamin D. No trials that included stratified analyses of fracture risk reduction by glucocorticoid use while being treated with bisphosphonates, raloxifene, denosumab, or calcium were found.			
Fracture Risk Reduction: Renal Function **SOE: Insufficient** In a subgroup analysis of the FIT alendronate trial of women with osteoporosis, alendronate reduced the risk of spine fractures and overall clinical fractures to a similar extent to those without reduced renal function. In a post hoc analysis of the HORIZON trial, antifracture effects of zoledronic acid were evaluated in relation to subgroups defined by age, body mass index, and renal function. The effects of zoledronic acid on reducing vertebral fracture risk were statistically significantly greater among women who were overweight or obese, and those who had creatinine clearance >60 ml/minute. However, no such treatment-factor interactions were apparent for nonvertebral or hip fractures. A post hoc analysis from the MORE raloxifene trial showed that irrespective	Denosumab recently received regulatory approval for the treatment of postmenopausal women with osteoporosis at high risk for fracture, with no dose adjustment in patients with renal impairment.[1]	See above.	The conclusions in this portion of the original systematic review are likely current. However new evidence is available.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
of kidney function (creatinine clearance level at baseline), raloxifene treatment was associated with a reduction in vertebral fractures, and no effect on nonvertebral fractures, compared to placebo. In a post-hoc analysis, a lower incidence of vertebral and nonvertebral fractures in teriparatide-treated versus placebo-treated patients was statistically consistent among patients with normal and impaired renal function. No trials that included stratified analyses of fracture risk reduction by renal function while being treated with ibandronate, risedronate, hormone replacement therapy, denosumab, vitamin D, or calcium were found.			
Fracture Risk Reduction: Timing of Initiation of Treatment **SOE: Low** A post hoc study focused on the timing of administration of zoledronic acid among men and women in the first 90 days after surgical hip fracture repair. Clinical fracture reduction was statistically significant, and was not significantly different among participants who had initiated zoledronic acid within 6 weeks (33%) compared with after 6 weeks (37%). No trials that included stratified	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
analyses of fracture risk reduction by timing of initiation of treatment while being treated with alendronate, ibandronate, risedronate, raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium were found.			
Fracture Risk Reduction: Cystic Fibrosis **SOE: Insufficient** A systematic review that included five trials of persons with cystic fibrosis (CF) who had not undergone lung transplants assessed the efficacy of bisphosphonates for fracture prevention in this group. Bisphosphonates increased BMD but had no significant effect on incident fracture in this population, a finding attributed, at least in part, to the small sample size and short duration of follow-up. No trials that included stratified analyses of fracture risk reduction by timing of initiation of treatment while being treated with raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Fracture Risk Reduction: High Risk Groups (including women with osteoporosis, transplant recipients, and high fall-risk populations) **SOE: High-Moderate**	In a three-year, randomized, placebo-controlled clinical trial in postmenopausal women with osteoporosis (n=7,808), patients who were treated with 60 mg of denosumab (vs placebo) every	Though one reviewer believed the conclusions of the original review to still be currently, the expert suggested a 2-year randomized, place-controlled, double-blinded study (n=181),	While the conclusions in this portion of the systematic review are likely current, one study found during the literature search reported that patients being treated with 60 mg of denosumab

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
Reduction in fracture risk for subjects treated with alendronate, risedronate, or vitamin D has been demonstrated in populations at increased risk for fracture due to conditions that increase the risk of falling including stroke with hemiplegia, Alzheimer's disease, and Parkinson's. There are limited and inconclusive data on the effect of agents for the prevention and treatment of osteoporosis on transplant recipients and patients treated with chronic corticosteroids. Alendronate, ibandronate, risedronate, teriparatide, raloxifene, zoledronic acid, and denosumab reduce the risk of fractures among high risk groups including postmenopausal women with osteoporosis.	six months for three years had fewer incidences of falling and concussions.[1]	of women with osteoporosis, aged ≥65, including those with cognitive impairment, immobility, and multimorbidity, who were living in nursing homes and assisted-living facilities. The treatment group received one 5-mg dose of zoledronic acid, and the control group received a placebo with daily calcium and vitamin D. While data regarding treatment on fracture risk was insufficient, the treatment group did improve BMD over two years. Participants in the treatment group had more incidences of multiple falls, but once the data was adjusted for baseline frailty, this rate was no longer significant.[6] The second reviewer believed the conclusions of the original review to still be current.	suffered fewer falls and concussions. This data point was not reported in the original systematic review.

Abbreviations: BMD=Bone Mineral Density; FRAX=Fracture Risk Assessment Tool; SOE=Strength of Evidence

Table 3. Key Question 3: What are the adherence and persistence with medications for the treatment and prevention of osteoporosis, the factors that affect adherence and persistence, and the effects of adherence and persistence on the risk of fractures?

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
Adherence and Persistence to Therapy **SOE: Moderate-High**	No studies were identified.	Both experts believed the conclusions of the original review to still be current.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
Eighteen RCTs reported rates of adherence to therapy. Twelve trials with bisphosphonates (five with alendronate, five with risedronate, and two with ibandronate) and two trials with denosumab reported high levels of adherence (majority with over 90% adherence). Two trials with raloxifene had adherence rates 65-70%. There is evidence from 58 observational studies, including 24 using U.S. data, that adherence and persistence with therapy with bisphosphonates, calcium, and vitamin D is poor in many patients with osteoporosis. One study described adherence with teriparatide. No studies describe primary nonadherence (i.e. nonfulfillment). It is important to note that adherence rates are higher in clinical trials than in real life and therefore in observational studies, which likely reflects the select populations and controlled environments in trials.			
Factors Affecting Adherence **SOE: Moderate-High** Based on evidence from 41 observational studies, many factors affect adherence and persistence with medications including, but not limited to: • Dosing frequency: Based on 20 observational studies, dosing	No studies were identified.	One reviewer believed the conclusions of the original systematic review to be current. This reviewer also suggested a prospective RCT[7] examining strategies to improve adherence, but this study does not meet inclusion criteria for the original systematic review.	The conclusions in this portion of the original systematic review are likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
frequency appears to affect adherence/persistence. Adherence is improved with weekly compared to daily regimens, but current evidence is lacking to show that monthly regimens improve adherence over that of weekly regimens; • Side effects of medications: Nine studies reported a significant effect of medication-associated adverse events on adherence or persistence, especially bisphosphonates (evidence from a systematic review and 15 out of 17 observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, nonvertebral or both); • Co-morbid conditions • Knowledge about osteoporosis • Cost Age, prior history of fracture, and concomitant medication use do not appear to have an independent association with adherence or persistence. The evidence on adherence to raloxifene, teriparatide, and other drugs and its association with fracture risk is insufficient to make conclusions.		The second reviewer believed the conclusions of the original review to be current.	
Association Between Adherence and Fracture Risk	No studies were identified.	Both experts believed the conclusions of the original	The conclusion in this portion of the original systematic review is

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
SOE: Low The evidence on adherence to raloxifene, teriparatide, and other drugs and its association with fracture risk is insufficient to make conclusions.		review to still be current.	likely current.

Abbreviations: RCT=Randomized Controlled Trial; SOE=Strength of Evidence; U.S.=United States

Table 4. Key Question 4: What are the short- and long-term harms (adverse effects) of the above therapies, and do these vary by any specific subpopulations?

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
Risk of PE **SOE: High** One RCT comparing risedronate vs placebo found no significant differences in risk for PE. Two RCTs show participants who took raloxifene were at higher odds for PE than did participants who took a placebo. No RCTs of alendronate, ibandronate, zoledronic acid, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting risk of PE were found.	No studies were identified.	One expert believed the conclusions to still be current, but suggested that using trials with bone mineral density as an endpoint may provide useful safety information. The second reviewer believes the conclusions of the original review to be current.	The conclusion in this portion of the original systematic review is likely current.
Risk of TE Events **SOE: High** One RCT comparing alendronate vs placebo found no significant differences in risk for TE.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
Four RCTs examining raloxifene vs placebo were examined. Individuals in the treatment group showed higher odds for venous TE. Estrogen and estrogen-progestin combination participants had higher odds of thromboembolic events than did placebo participants. No RCTs of ibandronate, risedronate, zoledronic acid, teriparatide, denosumab, vitamin D, or calcium reporting risk of TE were found.			
Risk of Cerebrovascular Accident (CeVA) **SOE: High** Three RCTs of raloxifene reporting CeVA were evaluated. A pooled analysis showed no significant risk for CeVA in the treatment groups. Estrogen and estrogen-progestin combination participants had higher odds of cerebrovascular accident (CeVA) than did placebo participants. One placebo-controlled trial of calcium found an increase in CeVA among users. No RCTs of bisphosphonates, teriparatide, denosumab, or vitamin D reporting risk of CeVA were found.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 2.5% of the 351 adverse events reported (approximately 9 reports) were cerebrovascular accidents.[4]	See above.	While the conclusions related to raloxifene, hormone replacement therapy, calcium, bisphosphonates, denosumab, and vitamin D are likely current, one study found during the literature search reported an increase in myocardial infarction while using teriparatide, while the evidence from the original systematic review was insufficient.
Risk of Serious Cardiovascular Events	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
SOE: Not Reported A pooled analysis of 16 trials showed a small but significant increase in serious cardiovascular adverse effects for raloxifene compared to placebo. No RCTs of bisphosphonates, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting serious cardiovascular events (not death) were found.			likely current.
Risk of Acute Coronary Syndrome **SOE: Moderate** Three RCTs comparing raloxifene vs placebo found no significant differences in risk of acute coronary syndrome. No RCTs bisphosphonates, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting acute coronary syndrome were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Risk of Atrial Fibrillation **SOE: Insufficient** One RCT found no significant difference in risk for atrial fibrillation in individuals treated with raloxifene vs placebo. No RCTs of bisphosphonates, teriparatide, hormone replacement therapy, denosumab, vitamin D, or	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
calcium reporting atrial fibrillation were found.			
Risk of Myocardial Infarction **SOE: Low** A meta-analysis of 15 placebo-controlled trials of calcium identified a small but significant increase in the risk for myocardial infarction in pooled results of five trials that contributed patient-level data. Trial –level data showed a similar effect. However, professional and clinical response to this meta-analysis has pointed out multiple concerns that may result in biased results. Among other problems, the analysis excluded vitamin D + calcium co-administration; the study did not account for dietary vitamin D and calcium intake; and calcium supplementation compliance was poor. No RCTs on bisphosphonates, raloxifene, teriparatide, hormone replacement therapy, denosumab, or vitamin D reported an increase in myocardial infarction.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 2.5% of the 351 adverse events reports (approximately 9 reports) were myocardial infarctions.[4]	See above.	While the conclusions related to raloxifene, hormone replacement therapy, denosumab, vitamin D, and calcium are likely current, one study found during the literature search reported an increase in myocardial infarction while using teriparatide, while the evidence from the original systematic review was insufficient.
Risk of Cardiovascular (CV) Death **SOE: Not Reported** One RCT comparing zoledronic acid vs placebo found no significant differences. One RCT comparing risedronate vs placebo found no significant differences.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
One pooled OR for three studies showed no significant differences between raloxifene and placebo for risk of cardiovascular death. No RCTs of alendronate, ibandronate, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting CV death were found.			
Risk of Breast Cancer **SOE: High** One RCT on alendronate found no significant difference. Two RCTs studying raloxifene vs placebo reported no significant increase in risk for breast cancer. One trial showed a significant decrease in the risk of breast cancer after the discontinuation of menopausal hormone therapy. No RCTs of risedronate, ibandronate, zoledronic acid, teriparatide, denosumab, vitamin D, or calcium reporting risk of breast cancer were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Risk of Colon and GI Cancer **SOE: Not Reported** One large case control study of bisphosphonate (alendronate, risedronate, ibandronate, and	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
zoledronic acid) use and GI cancers in the UK found no significant differences in the risk for colorectal cancer between users of bisphosphonates and matched controls. No RCTs on raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting risk of colon cancer were found.			
Risk of Esophageal Cancer **SOE: Insufficient** Four large observational studies on the incidence of esophageal cancer among bisphosphonate users were found. A cohort study found no difference in the risk for esophageal cancer between cohorts. A case-control study that used the same database as the cohort study found that individuals with at least one prescription for oral bisphosphonates had a significantly increased risk for esophageal cancer. When pooled, two additional large observational studies found a significantly increased risk for esophageal cancer in the bisphosphonate-treated group. A case-control study found that individuals diagnosed with esophageal cancer had an increased likelihood of bisphosphonate use. A case-control study found no increased risk for esophageal cancer for bisphosphonate users.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
No RCTs of raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting the risk of esophageal cancer were found.			
Risk of Lung Cancer **SOE: Not Reported** One RCT on risedronate found no significant difference in the risk of lung cancer. No trials of alendronate, ibandronate, zoledronic acid, teriparatide, hormone placement therapy, denosumab, vitamin D, or calcium reporting risk of lung cancer were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Risk of GI Events (including nausea) **SOE: High** A pooled analysis showed alendronate had a slightly increased risk of mild upper GI events. Alendronate participants had higher odds of mild upper GI events in head-to-head trials vs. menopausal hormone therapy. Pooled analysis showed alendronate users to be at an increased risk for mild GI events in head-to-head trials vs denosumab. Two RCTs found no significant difference in the incidence of PUBs between raloxifene and placebo. One	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 5.4% of the 351 adverse events reports (approximately 19 reports) were nausea.[4]	See above.	While conclusions related to bisphosphonates, denosumab, raloxifene, vitamin D, and calcium are likely current, one study found during the literature search reported an increase in GI events and nausea while using teriparatide, while the evidence from the original systematic review was insufficient.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
RCT found no significant difference in the incidence of mild GI events between raloxifene and placebo. One placebo-controlled trial showed an increase in reflux and esophageal complaints as well as other mild upper GI adverse events with use of denosumab. One trial assessing vitamin D reported no significant differences between treatment and placebo groups regarding GI adverse events. No trials of ibandronate, risedronate, zoledronic acid, teriparatide, or calcium reporting risk of lung cancer were found.			
Risk of Arthritis and Arthralgia **SOE: High** Pooled analysis of two RCTs comparing alendronate vs placebo showed a decreased risk for arthritis and arthralgia in the treated group. Analysis of four pooled trials comparing zoledronic acid vs placebo reported an increased risk of arthritis and arthralgia in the treated group. One RCT of ibandronate vs placebo found no significant difference. Five RCTs of risedronate vs placebo found no significant differences.	A double-blind RCT (n=143) compared the use of raloxifene at 60 mg/day or 120 mg/day to a control group receiving supplements of calcium (750 mg/day) and vitamin D (400 IU/day) in postmenopausal osteoporotic women (mean age=68.4). Results show significant incidences of arthralgia (p=0.027).[5]	See above.	This portion of the systematic review may not be current due to one study identified by our literature search which found an increased risk of arthritis and arthralgia while using raloxifene, while one placebo-controlled study from the original systematic review reported no significant effect on reports of arthritis and arthralgia with use of raloxifene. Conclusions on all other treatments on risk of arthritis and arthralgia are likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
In two head-to-head trials of alendronate vs denosumab, alendronate was significantly less likely to be associated with arthritis and arthralgia. One placebo-controlled study found no significant effect on reports of arthritis and arthralgia with use of raloxifene. No RCTs of teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting arthritis and arthralgia were found.			
Risk of Myalgia, Cramps, and Limb Pain **SOE: Moderate** Pooled analysis of two trials comparing ibandronate vs placebo showed an increase risk for myalgia, cramps, and limb pain in the treatment group. Pooled analysis of six trials comparing zoledronic acid vs placebo showed an increase risk of myalgia, cramps, and limb pain in the treatment group. A pooled analysis of ten trials found an increased risk with raloxifene for myalgia, cramps, and limb pain. No RCTs of alendronate, risedronate, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting myalgia, cramps, or	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
limb pain were found.			
Risk of Osteonecrosis **SOE: High** One trial, one post hoc analysis of three trials, two large observational studies, and a review of 2,408 cases of osteonecrosis of the jaw in patients taking bisphosphonates for osteoporosis prevention or treatment found that the incidence of osteonecrosis of the jaw in this group was small, ranging from less than one to 28 cases per 100,000 person-years of treatment. No RCTs on raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reported an increase in osteonecrosis.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Risk of Atypical Subtrochanteric Fractures of Femur **SOE: Low** Limited data from clinical trials and observational studies (a post-hoc analysis, a case series, and a task force report form the American Society of Bone and Mineral Research) support a possible association between bisphosphonate use and atypical subtrochanteric fractures of the femur. Data are not consistent; nevertheless these data were sufficient for FDA to issue a warning regarding this possible adverse event.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
No RCTs on raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reported an increase in atypical subtrochanteric fractures of the femur.			
Adverse Fracture Healing **SOE: Not Reported** One post hoc analysis showed no association between the timing of infusion of zoledronic acid and delayed fracture healing. One nested case-control study showed an association between bisphosphonate uses among individuals with nonunion humeral fractures found an increase in odds of nonunion fractures among patients who took bisphosphonates in the post-fracture period regardless of prior history of osteoporosis or fracture. No RCTs on raloxifene, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium vs placebo reported an increase in adverse fracture healing.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Risk of Hypercalcemia **SOE: Moderate** Teriparatide-treated participants showed a significant increase in hypercalcemia, according to a pooled analysis of three placebo-controlled trials.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
No RCTs comparing the effects of bisphosphonates, raloxifene, hormone replacement therapy, denosumab, vitamin D, or calcium reporting a risk of hypercalcemia were found.			
Risk of Hypercalciuria **SOE: Not Reported** One placebo-controlled trial of vitamin D showed an increased risk for hypercalciuria in the treatment group. No RCTs comparing the effects of bisphosphonates, raloxifene, teriparatide, hormone replacement therapy, denosumab or calcium reporting a risk of hypercalciuria were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Risk of Hot Flashes **SOE: High** A pooled analysis of eight placebo-controlled trials found an increased risk with raloxifene of hot flashes. No RCTs of bisphosphonates, teriparatide, hormone replacement therapy, denosumab, vitamin D, or calcium reporting hot flashes were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Risk of Headaches and Dizziness **SOE: Moderate** A pooled analysis of two trials of teriparatide found an increased risk of headaches.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 4.3% of the 351 adverse events	See above.	While conclusions related to teriparatide, hormone replacement therapy, denosumab, vitamin D, and calcium are likely current, one study found during the literature search reported an increase in

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
No RCTs of bisphosphonates, raloxifene, hormone replacement therapy, denosumab, vitamin D, or calcium reporting headaches and/or dizziness were found.	reports (approximately 15 reports) were headaches.[4] A double-blind RCT (n=143) compared the use of raloxifene at 60 mg/day or 120 mg/day to a control group receiving supplements of calcium (750 mg/day) and vitamin D (400 IU/day) in postmenopausal osteoporotic women (mean age=68.4). Compared to control, raloxifene was associated with more dizziness in non-hypotensive patients (p=0.024).[5]		dizziness in non-hypotensive patients while using raloxifene, while the evidence from the original systematic review was insufficient.
Risk of Rash **SOE: High** A pooled analysis of four trials of denosumab found an increased risk of rash but no increase in the risk for injection-site reactions. No RCTs of bisphosphonates, raloxifene, teriparatide, hormone replacement therapy, vitamin D, or calcium reporting rash were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Risk of Hypocalcemia **SOE: Moderate** A small number of clinical trials have reported an increased risk of hypocalcemia in patients treated with alendronate and zoledronic acid. No RCTs of ibandronate, risedronate, raloxifene, teriparatide, hormone	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
replacement therapy denosumab, vitamin D, or calcium reporting hypocalcemia were found.			
Risk of Infection **SOE: High** A pooled analysis of four trials of denosumab found an increased risk for infection in the treatment group. No RCTs of bisphosphonates, raloxifene, teriparatide, hormone replacement therapy, vitamin D, or calcium reporting infection were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.
Risk of Death **SOE: Not Reported** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of death were not included in the original review.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 4.1% of the 351 adverse events reports (approximately 14 reports) were death.[4]	See above.	This portion of the systematic review may not be current due to one study identified by our literature search which found an increased risk of death while using teriparatide, not previously reported in the original systematic review.
Transient Ischemic Attack **SOE: Insufficient** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of transient ischemic were not included in the original review.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 4.1% of the 351 adverse events reports (approximately 14 reports) were transient ischemic attack.[4]	See above.	This portion of the systematic review may not be current due to one study identified by our literature search which found an increased risk of transient ischemic attack while using teriparatide, while the evidence from the original systematic review was insufficient.
Risk of Arrhythmia **SOE: Insufficient** RCTs that directly compared the short- and long-term harms of the	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18	See above.	This portion of the systematic review may not be current due to one study identified by our literature search which found an increased risk of arrhythmia

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
aforementioned pharmacotherapies and the risk of arrhythmia were not included in the original review.	months of teriparatide treatment. 2.5% of the 351 adverse events reports (approximately 9 reports) were arrhythmias.[4]		while using teriparatide, while the evidence from the original systematic review was insufficient.
Risk of Dyspnea **SOE: Insufficient** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of dyspnea were not included in the original review.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 2.5% of the 351 adverse events reports (approximately 9 reports) were dyspnea.[4]	See above.	This portion of the systematic review may not be current due to one study identified by our literature search which found an increased risk of dyspnea while using teriparatide, while the evidence from the original systematic review was insufficient.
Risk of Hypertension **SOE: Insufficient** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of hypertension were not included in the original review.	A prospective observational study (n=1,576) documented clinical fracture and back pain in postmenopausal women with severe osteoporosis during 18 months of teriparatide treatment. 2.5% of the 351 adverse events reports (approximately 9 reports) were hypertension.[4]	See above.	This portion of the systematic review may not be current due to one study identified by our literature search which found an increased risk of hypertension while using teriparatide, while the evidence from the original systematic review was insufficient.
Risk of Hypotension **SOE: Insufficient** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of hypotension were not included in the original review.	A double-blind RCT (n=143) compared the use of raloxifene at 60 mg/day or 120 mg/day to a control group receiving supplements of calcium (750 mg/day) and vitamin D (400 IU/day) in postmenopausal osteoporotic women (mean age=68.4). There was a 6 mmHg decrease in systolic blood pressure in groups using raloxifene (p=0.028). None of the patients who reported dizziness were found to be hypotensive.[5]	See above.	This portion of the systematic review may not be current due to one study identified by our literature search which found an increased risk of hypotension while using raloxifene, while the evidence from the original systematic review was insufficient.
Risk of Dermatological Conditions	In a three-year, randomized,	See above.	This portion of the systematic

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
SOE: Insufficient RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of dermatological conditions were not included in the original review.	placebo-controlled clinical trial in postmenopausal women with osteoporosis (n=7,808), patients who were treated with 60 mg of denosumab (vs placebo) every six months for three years had more incidences of eczema and cellulitis.[1]		review may not be current due to one study identified by our literature search which found an increased risk of dermatological conditions while using denosumab, while the evidence from the original systematic review was insufficient.
Risk of Falling **SOE: Insufficient** RCTs that directly compared the short- and long-term harms of the aforementioned pharmacotherapies and the risk of dermatological conditions were not included in the original review.	In a three-year, randomized, placebo-controlled clinical trial in postmenopausal women with osteoporosis (n=7,808), patients who were treated with 60 mg of denosumab (vs placebo) every six months for three years had fewer incidences of falling and concussions.[1]	See above.	This portion of the systematic review may not be current due to one study identified by our literature search which found a decreased risk of falling while using denosumab, while the evidence from the original systematic review was insufficient.

Abbreviations: CVA=Cerebrovascular Accident; FDA=Food and Drug Administration; GI=Gastrointestinal; SOE=Strength of Evidence

Table 5. Key Question 5a: How often should patients be monitored (via measurement of bone mineral density) during therapy?

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
BMD Monitoring **SOE: Insufficient** No RCTs that directly compared various schedules of serial BMD monitoring during osteoporosis pharmacotherapy in relation to optimal fracture prediction were found.	No studies were identified.	Both experts believed the conclusions of the original review to still be current.	The conclusion in this portion of the original systematic review is likely current.
BMD Monitoring Predicting Anti-fracture Benefits During Pharmacotherapy **SOE: High** Studies from the Fracture Intervention	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
Trial (FIT) of alendronate vs. placebo (5 mg daily for the first two years, then 10 mg/day) among postmenopausal women showed that among participants taking at least 60% of assigned study medication, women who gained 0% to% of BMD after 1-2 years during treatment had a decrease in vertebral risk of 51% after 3-4 years of follow-up. However, women who had lost 0% to 4% of lumbar spine BMD during alendronate therapy had a 60% lower risk of vertebral fractures compared to their counterparts assigned to placebo. The study concluded that monitoring bone mineral density in postmenopausal women in the first three years after starting treatment with a potent bisphosphonate is unnecessary and may be misleading. A study examining participants assigned 2.5 mg of risedronate vs 5 mg of risedronate per day, incidence of nonvertebral fractures during three years of follow up was not different between women whose spine BMD increased. A similar study found no significant difference in risk of nonvertebral fractures between women whose femoral neck BMD increased or decreased. Thus, greater increases in BMD did not necessarily predict greater decreases in vertebral fracture risk.			

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
A post hoc pooled analysis of two RCTs, increases in hip and lumbar spine BMD during oral or intravenous ibandronate administration were statistically significantly associated with vertebral fracture rate. However, changes in total hip and lumbar spine BMD explained only 23%-37% of the antifracture effect at 2 and 3-year follow up. Raloxifene The reduction of risk for fracture analyzed in the three year MORE trial on raloxifene showed no difference in risk fracture regardless of the amount of change in lumbar spine BMD at three years. Irrespective of femoral neck and lumbar spine BMD, raloxifene decreased risk of new fractures by 38% in year one and 41% by year three. In the Fracture Prevention Trial (teriparatide 20 or 40 µg/day vs. placebo in postmenopausal women), women who lost greater than 4% at the femoral neck during the first 12 months of teriparatide treatment had significant reductions in vertebral fracture risk compared to placebo during a median of 19 month follow-up. Compared to women assigned to placebo, the decrease in vertebral fracture risk in women assigned to teriparatide was similar across categories of femoral neck BMD change from baseline to 12 months. Vertebral fracture risk was			

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
decreased among women who lost femoral neck BMD during teriparatide therapy. Among women assigned to teriparatide, increases in spine BMD accounted for 30% to 41% of the reduction in vertebral fracture risk. Greater increases in BMD did not necessarily predict greater decreases in fracture risk. No studies reporting effect of BMD monitoring on antifracture benefits during pharmacotherapy for ibandronate, zoledronic acid, denosumab, menopausal hormone therapy, vitamin D, or calcium were found.			
Ability to Predict Anti-fracture Events in Various Pharmacotherapies **SOE: Insufficient** No RCTs that directly compared the ability of monitoring to predict anti-fracture effects among various pharmacotherapies were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Abbreviations: BMD=Bone Mineral Density; SOE=Strength of Evidence

Table 6. Key Question 5b: How does the antifracture benefit vary with long-term continued use of pharmacotherapy?

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
Long-Term Use of Pharmacotherapies on Fracture Risk **SOE: Moderate**	No studies were identified.	Both experts believed the conclusions of the original review to still be current.	The conclusion in this portion of the original systematic review is likely current.

Conclusions From Original Systematic Review Link to Report	Literature Analysis (May 2016)	Expert Opinion	Surveillance Assessment
One large RCT showed that after 5 years of initial alendronate therapy, vertebral fracture risk and nonvertebral fracture risk were lower if alendronate was continued for an additional 5 years instead of discontinued. No studies reporting effect of long-term use of ibandronate, risedronate, zoledronic acid, raloxifene, teriparatide, menopausal hormone therapy, denosumab, vitamin D, or calcium on fracture risk were found.			
Long-Term Use of Pharmacotherapies and BMD on Fracture Risk **SOE: Low** A post hoc analysis of a large RCT showed that after 5 years of initial alendronate therapy, there were statistically significant nonvertebral fracture risk reductions for women who at baseline had no vertebral fracture but had a BMD score of –2.5 or less. No studies reporting effect of long-term use of ibandronate, risedronate, zoledronic acid, raloxifene, teriparatide, menopausal hormone therapy, denosumab, vitamin D, or calcium and BMD on fracture risk were found.	No studies were identified.	See above.	The conclusion in this portion of the original systematic review is likely current.

Abbreviations: BMD=Bone Mineral Density; RCT=Randomized Controlled Trial; SOE=Strength of Evidence

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